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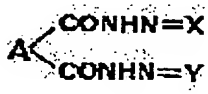
(54) PORPHYRIN DIMER AND ITS USE

(57)Abstract:
PURPOSE: To provide a new compound useful as a sensitizer for photodynamic diagnosis and therapy, a contrasting agent for the diagnosis and treatment of cancer and for nuclear magnetic resonance and a diagnostic agent for nuclear magnetic resonance.
CONSTITUTION: The compound of formula I [A is (CH2)n ((n) is 0-8) or phenylene; X and Y are porphyrin or metal porphyrin of formula (R1 and R2 are OH or residue produced by removing H from an amino acid; Z is bonding site to the compound of formula I; M is 2H, Mn, Cu or Zn), etc.], e.g. bis-(photoprotoporphyrin)hydrazone oxalate. The compound of formula I can be produced by reacting porphyrin derivative supporting a ketone or an aldehyde with a dicarboxylic acid bishydrazide in the presence of a condensing agent.



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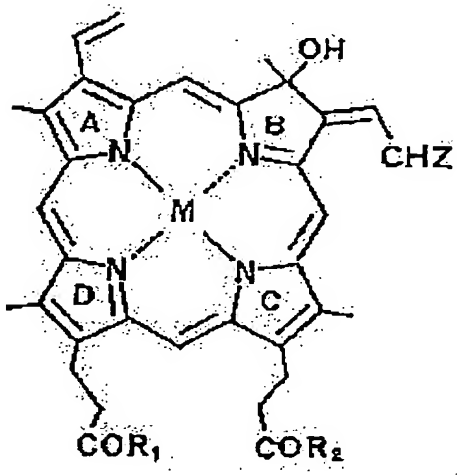

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[JP,06-080671,A]

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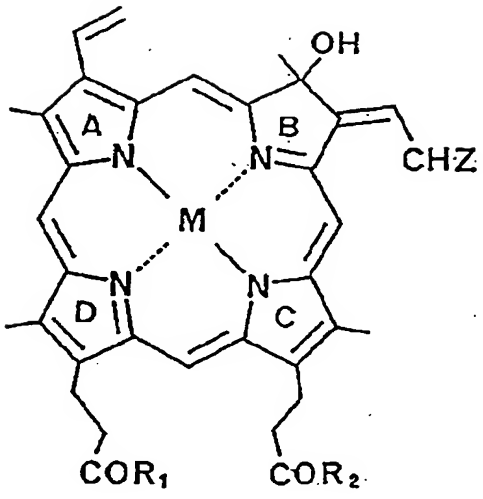
CLAIMS

[Claim(s)]

[Claim 1] General formula (I) A among a-izing 1[type n (CH2) or a phenylene group, It is the porphyrin or metalloporphyrin (however, among a formula) which shows n by X and shows 0-8, and Y by ** 2, ** 3, or ** 4. in R1 and R2, OH or the residue excluding hydrogen from amino acid, and R3 show COOCH3, respectively, and H or M shows 2H, and Mn, Cu or Zn -- the porphyrin dimers shown by residue] excluding oxygen from the ketone or aldehyde of a side chain, or those metal complexes. (However, Z of a porphyrin frame side chain shows a binding site with ** 1 among a formula.) Moreover, the functional group of the side chain of B ring also contains the position isomer which interchanged, respectively among [A] four pyrrole rings of a porphyrin frame.

[Formula 1]

[Formula 2]



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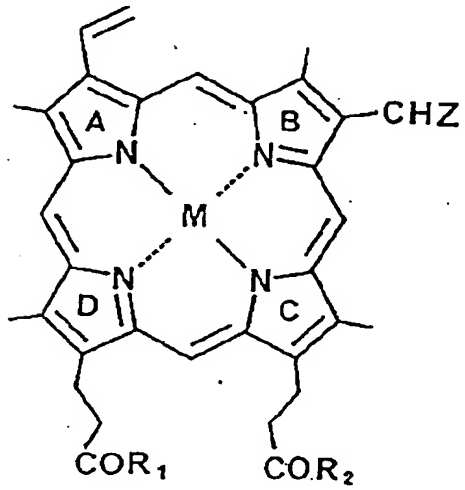

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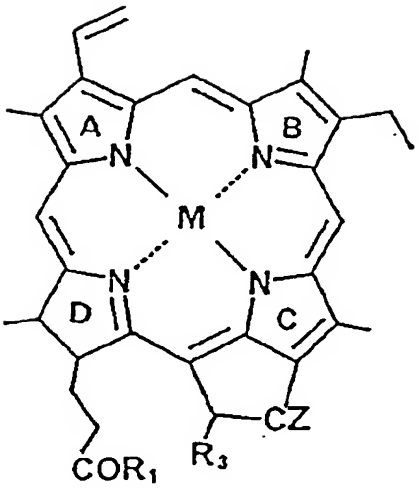


[Claim 2] The object for an optical physicochemical diagnosis and/or the sensitizer for a therapy which consist of a porphyrin according to claim 1 and a metalloporphyrin compound.

[Claim 3] The sensitizer for optical physical chemistry according to claim 2 used for a diagnosis and/or therapy of cancer.

[Claim 4] The contrast medium for nuclear magnetic resonance which consists of a Mn metalloporphyrin compound according to claim 1.

[Claim 5] The diagnostic agent for nuclear magnetic resonance according to claim 4 used for IMEJINGU of cancer.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the drugs which use a porphyrin dimer, its application, a new porphyrin (non-metal complex-non-metal complex compound), a metalloporphyrin (metal complex-metal complex compound) dimer, and a porphyrin-metalloporphyrin (non-metal complex-metal complex compound) derivative for a diagnosis and therapy of the cancer by the sensitizer and the contrast medium for nuclear magnetic resonance, and/or the optical physical chemistry for the object for an optical physicochemical diagnosis, and a therapy which are made into an active principle, and the diagnosis by nuclear magnetic resonance especially.

[0002]

[Description of the Prior Art] The optical physicochemical fluorescence diagnosis and the therapy [Photodynamic Diagnosis and Therapy (PDDT)] are performed as new diagnosis and cure for cancer. After this prescribing a porphyrin compound of a certain kind for the patient by approaches, such as an intravenous injection, and making it hold it in a cancer organization, laser light is irradiated, and it carries out the fluorescence diagnosis only of the cancer organization alternatively, and it destroys. PDDT uses two properties in which the time amount held in the cancer organization of a porphyrin has the property in which it is long compared with normal tissue, and a photosensitization operation. In the past 13 years, 3000 or more people are treated for the malignant tumor by PDDT all over the world, and it was established as one of the cancer treatments. Retina cancer, skin carcinoma, an esophagus cancer, superficialness vesical cancer, early lung cancer, etc. are going across the cancer type it is reported by PDDT that good treatment results are variably. Moreover, it came to be used also for the fluorescence diagnosis which used the endoscope recently.

[0003] The drugs currently used for current [PDDT] are mainly the dimers of a hematoporphyrin derivative (HPD) and its ether object, and/or an ester object. HPD is mixture which carries out vitriolization in an acetic acid of the hematoporphyrin, and is processed and obtained by 0.1 moreN sodium hydroxide. The hydrophobic high component of HPD is mainly included, with HPD, a dimer is complicated mixture and its active ingredient is unknown. Moreover, since the component ratio is not fixed, a curative effect is very unstable.

[0004] On the other hand, it considers as the new porphyrin derivative for PDDT, and, for Kessel and others, Pandey and others is [Dougherty and others] Tetrahedron to Photochem.Photobiol. and 53,475 (1991) in a U.S. Pat. No. 4649151 number (1987) about a porphyrin dimer. Collman and others is indicating to Lett., and 29 and 4657 (1988) J.A.C.S., and 105 and 2699 (1983). We also examined many things and have indicated to Agric.Biol.Chem., and 55 and 2441 (1991). However, utilization was [in / with the above-mentioned compound / the field of composition, stability, water solubility, and non-phototoxicity] difficult for using as a sensitizer for PDDT.

[0005] Moreover, there is also a problem of organization permeability of the laser light used for PDDT. The maximum absorption wavelength is 630nm and the molar extinction coefficient of HPD or its dimer is also as low as 3000. With 630nm light, organization permeability will be bad and will be limited to the surface cancer whose curative effect of PDDT is 5-10mm.

[0006] On the other hand, there is a problem also in laser equipment. The dye laser

present most often used has bad stability, and the handling on employment is difficult for it. Employment will become quite easy if the titanium sapphire laser which attracts attention recently is used. However, if this laser is used, it will be restricted to 670nm or more absorption wavelength of 600nm or less, and it can apply to neither HPD with the absorption wavelength near 630nm, nor its dimer.

[0007] Furthermore, causing photosensitivity temporary as a side effect of drugs is known. For this reason, after medication, a patient must be confined in a dark place for a long period of time so that normal tissues, such as the skin, may not be destroyed in a photosensitization operation. Since the elimination rate from normal tissue is slow, when long, as for HPD and its dimer, photosensitivity may remain six weeks or more. Development of the new drugs which the drugs by which current use is carried out are holding the trouble of such many, and replace HPD and its dimer is desired strongly. Then, the compound which is a single compound as what conquers the fault which the above-mentioned drugs have, and has absorption in a long wavelength field (650-800nm) more is proposed as a drug of the second generation. It inquires as drugs which various compounds, such as ring escape mold porphyrins, such as porphyrins, such as aza-porphyrins, such as a current phthalocyanine, and chlorin bacteriochlorin, and TEKISAFIRIN, replace with HPD or its dimer. Moreover, said HPD and its dimer are used together as both drugs not only as the object for the therapy of cancer but as an object for a fluorescence diagnosis. However, properly speaking, therefore as for the object for a therapy, and the object for a diagnosis, the phototoxicity which the drugs have should have been separated, and a non-phototoxicity (non-phosphorescence) fluorescence diagnostic agent was desired strongly.

[0008]

[Problem(s) to be Solved by the Invention] this invention persons are single components and the good accumulation nature to stability and a cancer organization has been maintained. From normal tissue, an elimination rate is quick, and when applying as a fluorescence diagnostic agent, it is non-phototoxicity (the life time of fluorescence is long). a compound with a short phosphorescence life is in criteria -- moreover it could do, when getting, it looked for the porphyrin derivative which can use titanium sapphire laser (670nm or more wavelength of 600nm or less), and various researches were repeated for the purpose of offering the photosensitizer suitable for PDDT.

[0009]

[Means for Solving the Problem] Consequently, when the chlorins obtained by carry out synthetic derivatization from the protoporphyrin of the blood origin in front

******** (Japanese Patent Application No. No. 323597 [three to]) or FEOHOBAIDO of the chlorophyll origin be used as the dimer through a spacer of a certain kind, it found out have the absorption wavelength of 670nm or more for eccritic [better than the accumulation nature and normal tissue which be excellent in the single component to the cancer organization] moreover, and have the good PDDT effectiveness. Furthermore, it succeeded also in composition of the dimer of a non-metal complex-non-metal complex compound, a metal complex-metal complex compound, and a non-metal complex-metal complex compound by combining these reactions. Especially, as for the semimetal compound of a non-metal complex-metal complex dimer of a certain kind, the property of non-phototoxicity (non-phosphorescence) fluorescence existed.

[0010] Moreover, like front ********, when this invention persons analyzed these dimers and the ultraviolet absorption (UV) spectrum of the mixture of albumin, they found that the trend of a spectrum had led to the compatibility to a positive direction, i.e., a specific organ, especially cancer.

[0011] On the other hand, this invention persons are in the middle of [this] researches and developments, and found out the evaluation approach of photosensitized oxidation using the system of a dansyl methionine substrate. When using this approach, thin-layer chromatography (TLC) and high performance chromatography (HPLC) have estimated the reactant existence and the strength to the light in a dimer simple. In addition, the value by this appraisal method showed the merits and demerits of a phosphorescence life, and a good correlation.

[0012] On the other hand, if fluorescence intensity is measured as stated also in the former application specification (JP,2-138280,A), various properties can prove physicochemically. Therefore, when there is no phosphorescence life in a porphyrin with fluorescence or short metalloporphyrin was made to combine, it was thought that a non-phototoxicity fluorescence diagnostic agent was born. The main things of the measurement result are shown in Table 1. When the above is taken into consideration, for a non-metal complex-non-metal complex compound, it is ******** also in the dimer of this invention that a metal complex-metal complex compound can use a non-metal complex-metal complex compound for a therapy according to an application as drugs for a fluorescence diagnosis the object for a therapy or for a nuclear-magnetic-resonance diagnosis (MRI).

[0013]

[Table 1]

化合物名
MHP
PhotofrinII®
(2) MHP_2
(3) $AH_2(P-Asp)_2$
(4) $mPH_2(P-Asp)_2$
(5) $pPH_2(P-Asp)_2$
(6) $MH_2(Mn-P)_2$
(14) MH (Mn-P) (P)
(16) AH (Mn-P-Asp) (P-Asp)
(17) AH (Cu-P-Asp) (P-Asp)
(20) mPH (Mn-P) (P-Asp)
(22) MH (Cu-P) (P-Asp)
(24) mPH (Cu-P) (P-Asp)

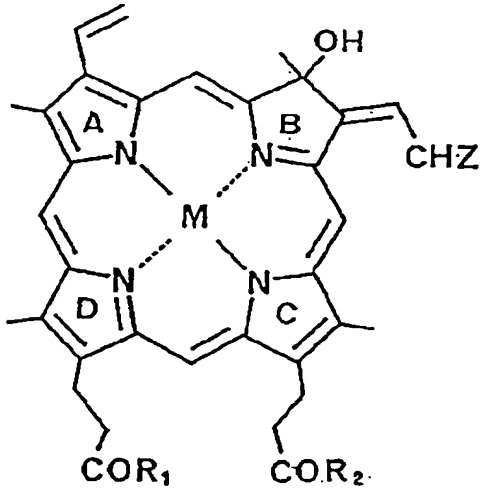
[0014] This invention is completed based on the above-mentioned knowledge, and the summary is a general formula. (I) Inside of a-izing 5[type, A is the porphyrin or metalloporphyrin (however, among a formula) which shows n (CH2) or a phenylene group, and n by X, and shows 0-8, and Y by ** 6, ** 7, or ** 8. in R1 and R2, OH or the residue excluding hydrogen from amino acid, and R3 show COOCH3, respectively, and H or M shows 2H, and Mn, Cu or Zn -- the porphyrin dimers shown by residue] excluding oxygen from the ketone or aldehyde of a side chain, or those metal complexes. (However, Z of a porphyrin frame side chain shows a binding site with ** 1 among a formula.) Moreover, the functional group of the side chain of B ring also contains the position isomer which interchanged, respectively among [A] four pyrrole rings of a porphyrin frame.

[0015]

[Formula 5]

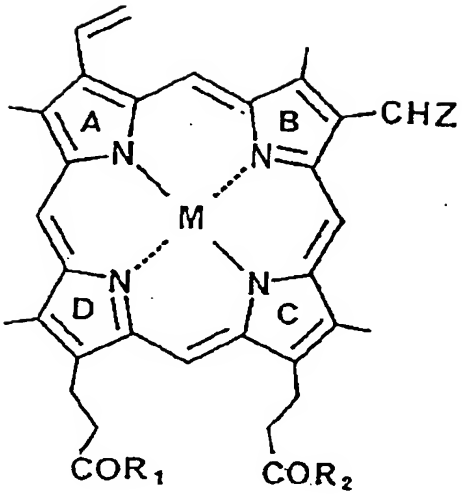
[0016]

[Formula 6]



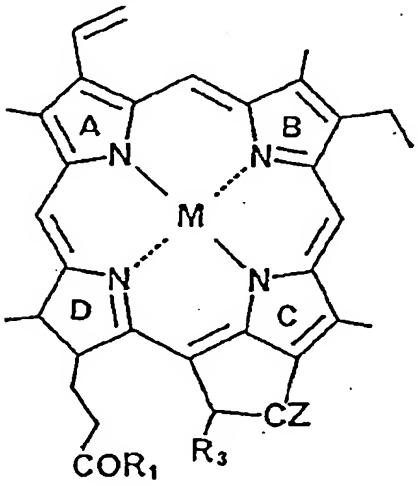
[0017]

[Formula 7]



[0018]

[Formula 8]



[0019] The word which the word "amino acid" amino acid [which was used about the semantics of each above-mentioned notation] Becoming a "phenylene group" phenylene group [an essential amino acid and] Turns into means meta and a para-position binding site.

[0020] The various porphyrin dimers of this invention can be manufactured by the very thing conventionality. If X and Y corresponding to a general formula (I) are in a porphyrin dimer (non-metal complex-non-metal complex compound) of the same kind, what has R1, R2, or R3 is constituted (process a), and subsequently to the following process b it progresses, and it accomplishes with a dimer of the same kind to a single step through a spacer, and the obtained porphyrin dimer is made to hydrolyze

(process c). Moreover, a sequential reaction may not necessarily be carried out with a process (a), (b), and (c), for example, as shown in a process (b), (a), (c) or a process (a) and (c), and (b), the order of a process may replace. In addition, X and Y may compound a dimer of the same kind in two steps which pass through a process (e) so that it may state later.

[0021] On the other hand, if X and Y corresponding to a general formula (I) are in a metalloporphyrin dimer (metal complex-metal complex compound) of the same kind, what has M first is constituted (process d), subsequently this is derivatized like the above-mentioned, and a sequential reaction is carried out with a process (a), (b), and (c). Moreover, even if the order of a process is not necessarily fixed, as the point described, the order of a process may change.

[0022] On the other hand, if X and Y corresponding to a general formula (I) are in a porphyrin-metalloporphyrin dimer (non-metal complex-metal complex compound) of a different kind, what has M first is constituted (process d), and the porphyrin which has R1, R2, and R3 separately is constituted (process a). Then, a spacer is made to combine with either among the porphyrin derivatives obtained at Process d or Process a (process e). Subsequently, the porphyrin compound obtained from Process a or Process d is made to react, a different-species porphyrin dimer is obtained in two steps, and it progresses to Process c below. Moreover, the different-species porphyrin dimer (non-metal complex-non-metal complex compound) by the difference in a porphyrin side chain as well as this is compounded in two steps except constituting what has M.

[0023] A configuration process (a and d) can perform this by the conventional approach indicated by J.E.Falk work [Porphyrins and Metalloporphyrins] (Elsevier issue, 1975), D.Dolphin work [The Porphyrins] (Academic Press issue, 1978), etc.

[0024] For example, what is the porphyrin compounds which have R1, R2, and R3 corresponding to (I), and those metal complexes should just prepare this according to the approach indicated by JP,61-7279,A, JP,61-83185,A, the patent official report No. 13997 [Showa 63 to], JP,2-76881,A, JP,2-138280,A, JP,4-59779,A, and Japanese Patent Application No. No. 323597 [three to]. That is, about a process (a), the joint process of amino acid residue can be given via a chlorin chemically-modified degree (photograph protoporphyrin) using photochemical reaction, and this can be performed. About a process (d), this is usually performed using a metaled chloride, acetate, a sulfate, a nitrate, etc. As a metaled class, Zn with the long phosphorescence life effectiveness, Mn, Cu, Fe which have the compaction effectiveness conversely, etc. are mentioned. Moreover, this metal installation process (d) may not ask the (a) or (b)

process order, but may prepare it if needed. Instead of compounding artificially, this may be extracted from a natural resource like vegetation or an animal.

[0025] Next, the chlorin compound constituted as mentioned above and/or its complex, and a FEOHOBAIDO compound are given to a condensation process (b) or (c). Namely, protoporphyrin 1-hydroxy-2-formyl ethylidene-protoporphyrin obtained by carrying out photochemical reaction processing of the dimethyl ester (henceforth PP-Me) Dicarboxylic acid bis-hydrazide derivative is made to react to dimethyl ester (henceforth photograph protoporphyrin dimethyl ester and P-Me) and/or its complex, and the FEOHOBAIDO derivative that carried out isolation purification from the green leaf natural product, and the target condensation product porphyrin compound is manufactured. This thing can perform this by the conventional approach indicated by the general organic chemistry experiment in the letter ([addition or a condensation reaction] with a hydrazone, a ketone, or an aldehyde compound). In addition, in any case, use of a reaction accelerator like a dehydrating agent or a deoxidizer or a condensing agent may also be suitably taken into consideration.

[0026] Hereafter, the example of representation is given and preparation of a porphyrin dimer compound (I) is explained still more concretely. X and Y for example, in the case of a porphyrin dimer (namely, a non-metal complex-non-metal complex compound and a metal complex-metal complex compound) of the same kind a ketone, an aldehyde support porphyrin derivative, or its metal complex -- dicarboxylic acid bis-hydrazide (for example, oxalic acid dihydrazide --) Malonic-acid dihydrazide, adipic-acid dihydrazide, isophthalic acid dihydrazide, Terephthalic-acid dihydrazide etc. is made to react using condensing agents (for example, an acid, alkali, etc.) suitably in solvents, such as THF, and the porphyrin dimer (I) of the same kind which made these bis-hydrazone the spacer is obtained by the single step. The following can be mentioned as the example.

[0027] (1) Oxalic acid-screw (photograph protoporphyrin) hydrazone (it is called the following OHP 2)

(2) Malonic-acid-screw (photograph protoporphyrin) hydrazone (it is called the following MHP2)

(3) A bis adipate (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following AH(P-Asp) 2]

(4) An isophthalic acid-screw (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following mPH(P-Asp) 2]

(5) A terephthalic-acid-screw (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following pPH(P-Asp) 2]

(6) A malonic-acid-screw (Mn-photograph protoporphyrin) hydrazone [it is called the following (Mn-P) MH 2]
(7) A bis adipate (Mn-photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following AH(Mn-P-Asp) 2]
(8) A bis adipate (Cu-photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following AH(Cu-P-Asp) 2]
(9) A bis adipate (Zn-photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following AH(Zn-P-Asp) 2]
(10) A bis adipate (SUPIROGURAFISU) hydrazone [it is called the following (SP) AH 2]
(11) A bis adipate (SUPIROGURAFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following AH(SP-Asp) 2]
(12) A bis adipate (FEOHOBAIDO) hydrazone [it is called the following AH(PPB) 2]
(13) A bis adipate (PIROFEOHOBAIJIRU -6, 7-bis-aspartic acid) hydrazone [it is called the following AH(pyroPPB-Asp) 2]
[0028] on the other hand, when X and Y are porphyrin dimers (namely, compound with which X differs from Y even if it is a non-metal complex-metal complex compound, the same non-metal, or the porphyrin dimer of a metal complex) of a different kind, a ketone, aldehyde support compounds, or those metal complexes are first reacted [in said dicarboxylic acid bis-hydrazide] using a condensing agent suitably in a solvent -- making -- X or Y -- the mono-hydrazone object which either combined is acquired. Subsequently, a ketone, aldehyde support compounds, or those metal complexes are made to react to the acquired mono-object like the above-mentioned, and a porphyrin dimer (I) of a different kind is obtained. The following can be mentioned as the example.
[0029] (14) A malonic-acid-monochrome (Mn-photograph protoporphyrin)-monochrome (photograph protoporphyrin) hydrazone [it is called Following MH (Mn-P) (P)]
(15) A malonic-acid-monochrome (Cu-photograph protoporphyrin)-monochrome (photograph protoporphyrin) hydrazone [it is called Following MH (Cu-P) (P)]
(16) An adipic-acid-monochrome (Mn-photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following AH (Mn-P-Asp) (P-Asp)]
(17) An adipic-acid-monochrome (Cu-photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following AH (Cu-P-Asp) (P-Asp)]
(18) An adipic-acid-monochrome (photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called

Following AH (P) and (P-Asp)]

(19) An adipic-acid-monochrome (Mn-photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following AH (Mn-P) (P-Asp)]

(20) An isophthalic acid-monochrome (Mn-photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following mPH (Mn-P) (P-Asp)]

(21) A terephthalic-acid-monochrome (Mn-photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following pPH (Mn-P) (P-Asp)]

(22) A malonic-acid-monochrome (Cu-photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following MH (Cu-P) (P-Asp)]

(23) An adipic-acid-monochrome (Cu-photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following AH (Cu-P) (P-Asp)]

(24) An isophthalic acid-monochrome (Cu-photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following mPH (Cu-P) (P-Asp)]

(25) A terephthalic-acid-monochrome (Cu-photograph protoporphyrin)-monochrome (photograph pro TOPORUFINIRU -6, 7-bis-aspartic acid) hydrazone [it is called Following pPH (Cu-P) (P-Asp)]

[0030] What is necessary is just to perform manufacture of the drugs pharmaceutical preparation of the porphyrin derivative by this invention by the the very thing well-known method, and to dissolve the derivative by this invention with the suitable buffer solution. The solubilizing agent (for example, organic solvent) which uses as a suitable additive, for example, can be admitted in physic, pH modifier (for example, an acid, a base, the buffer solution), a stabilizer (for example, ascorbic acid), an excipient (for example, glucose), an isotonizing agent (for example, sodium chloride), etc. may be blended.

[0031] the drugs by this invention -- the need as drugs for PDDT -- depending on the sufficient property, i.e., long phosphorescence life, case, a short phosphorescence life, non-phosphorescence fluorescence (there is no photoreaction only by fluorescence), the compatibility over albumin, a specific organ especially the specific accumulation nature to cancer, photoreaction nature, the optical killer cell effectiveness, absorption wavelength, water solubility, purity, etc. are satisfied enough. The good water solubility

of the drugs by this invention enabled manufacture of a high concentration solution (50mg/(ml)). Generally, in order to apply as drugs for PDDT, it is desirable to prescribe the drugs of this invention for the patient in the amount of 1mg – 10 mg/kg weight as the amount of 1mg – 5 mg/kg weight and drugs for MRI.

[0032]

[Function] The porphyrin dimer concerning this invention and its metal complex have the description on the chemical structure at the point of having used the bis-hydrazone derivative for the ketone and/or aldehyde residue of a porphyrin frame side chain as a spacer, and, as a result, demonstrate various physiological or pharmacological profiles.

[0033] A cancer cell is piled up alternatively and these porphyrins derivative has the slow elimination from a cancer cell. In addition, from a normal organ or a cell, since it is excreted promptly, damage is not done to them. Originally, although the thing of ****** of a porphyrin derivative had the strong operation to light, while it raised excretory [from normal tissue] by dimerizing a porphyrin derivative according to this invention, the derivative of it designed so that a phototoxic manifestation might be controlled as much as possible became possible. Moreover, since wavelength carried out the red shift by using a chlorin derivative, the degrees of ** of a curative effect were able to be measured. The porphyrin dimer and metal complex of this invention are useful as the object [as opposed to an organ especially specific cancer, or a specific malignant tumor based on these properties (cancer compatibility, non-phosphorescence fluorescence, non-phototoxicity, the optical killer cell effectiveness, absorption wavelength, water solubility)] for PDDT, or drugs for MRI.

[0034] An example is given and explained below. In addition, all the yield in an example is the values converted and calculated from P-Me and FEOHOBAIDO (it is called Following PPB) which are a start raw material.

[0035]

[Example]

Example Using P-Me2g compounded by the approach hung up over aspartic-acid derivatization JP,2-138280,A and JP,4-59779,A of one porphyrin, pyridine 50ml was added to this and it hydrolyzed with the conventional method with caustic alkali of sodium 10% after the dissolution. The citric-acid water solution extracted hydrolysis liquid under the chloroform after neutralization 20%. Vacuum concentration of the extract was carried out and photograph protoporphyrin (it is called Following P) 1.75g was obtained after reprecipitation by the ethyl-acetate-n-hexane. (Saponification of ester)

The whole quantity of obtained P was dissolved in the tetrahydrofuran, and it considered as the P-DCHA salt (2.0g) with the conventional method in dicyclohexylamine (DCHA). This DCHA salt is dissolved in chloroform 150ml, and it is an aspartic acid. 2g of dimethyl ester (AspMe) hydrochlorides was added, and you added water-soluble carbodiimide (WSC) 2g gradually to the bottom of churning, and made it react for 1.5 hours. Vacuum concentration of the chloroform layer was carried out for reaction mixture after rinsing liquid separation after the reaction (a reaction end point is checked in TLC). Reprecipitation and recrystallization are repeated in an ethyl-acetate-ether-n-hexane, the obtained concentrate is performed, and it is photograph pro TOPORUFINIRU of a dark green crystal. - 6, 7-bis-aspartic acid Tetramethyl ester (henceforth P-AspMe) was obtained. (1.2g, 42.4% of yield)

[0036] Example The approach hung up over Mn metal complex-ized JP,2-138280,A and JP,4-59779,A of 2 porphyrin compounds was improved and compounded. P-AspMe100mg obtained in P-Me3g and the example 1 was dissolved in the acetic acid, respectively, and manganese acetate was added, and it warmed at 50 degrees C, and was made to react under churning for 2 hours. After the reaction, the physiological saline was added to reaction mixture 0.9%, and precipitate was obtained separately. Reprecipitation is repeated for obtained sediment by the methanol-ethyl-acetate-n-hexane after rinsing desiccation, and it is Mn-photograph protoporphyrin of a dark brown crystal. Dimethyl ester (henceforth Mn-P-Me) and Mn-photograph PORUFINIRU -6, 7-bis-aspartic acid Tetramethyl ester (henceforth Mn-P-AspMe) was obtained separately. (2.8g and 90mg, 81.8% of yield, 34.7%)

[0037] Example The approach hung up over Cu metal complex-ized JP,2-138280,A and the example 1 of 3 porphyrin compounds was improved and compounded. P-AspMe150mg obtained in P-Melg and the example 1 was separately dissolved in the chloroform-methanol (2:1 v/v), respectively, copper acetate was added, and it was made to react for 30 minutes under churning at a room temperature. after the reaction (** -- green), chloroform was added to each reaction mixture, the physiological saline washed 0.9%, and vacuum concentration of the chloroform layer was carried out. Reprecipitation is repeated for the obtained residue in an ethyl-acetate-n-hexane, and it is Cu-photograph protoporphyrin of a dark green crystal. Dimethyl ester (henceforth Cu-P-Me) and Cu-photograph PORUFINIRU -6, 7-bis-aspartic acid Tetramethyl ester (henceforth Cu-P-AspMe) was obtained separately. (1g and 130mg, 91.0% of yield, 34.4%)

[0038] Example Tetrahydrofuran 150ml is added to synthetic P-Me500mg of 4 monomer objects, and 50ml of malonic-acid dihydrazide (it is called Following MH)

water solutions was dropped 1%, and it was made to react to the bottom of room temperature churning for 24 hours. Rinsing desiccation vacuum concentration of the reaction mixture was extracted and carried out with ethyl acetate after the reaction (migration of an Rf value is checked in TLC). The obtained concentrate (400mg) was given to the silica gel column chromatography, an ethyl-acetate-methanol (9:1) and (1:1) elution fractions were collected, and the solvent was distilled off. Each residue was recrystallized by the ethyl-acetate-n-hexane and the tetramethyl ester of the dimer object MHP2 of a dark brown crystal (2) and a monomer object malonic-acid-monochrome (photograph protoporphyrin dimethyl ester) hydrazone [it is called Following MH (P-Me)] were obtained separately. (50mg and 120mg, 4.6% of yield, 20.3%)

[0039] Example MH(P-Me)80mg obtained in the synthetic example 4 of the dimer of the same kind by 5 two-step method is dissolved in tetrahydrofuran 40ml, P-Me100mg and 0.2ml of acetic acids were added, and they were made to react to the bottom of room temperature churning for two weeks. After the reaction, the after [rinsing] chloroform extraction of the reaction mixture was carried out, it recrystallized with the ethyl-acetate-methanol after distilling off a solvent, and the tetramethyl ester of the dimer object MHP2 (2) made into the purpose was obtained. (100mg, 13.9% of yield)

[0040] Example P-AspMe100mg obtained in the synthetic example 1 of the dimer of the same kind by six single step methods was dissolved in tetrahydrofuran 25ml, adipic-acid dihydrazide (it is called Following AH) was added to the bottom of room temperature churning, and it was made to react for five days. After the reaction, the chloroform extraction of the reaction mixture was rinsed and carried out, reprecipitation was repeated in the tetrahydrofuran-ethyl-acetate-n-hexane and the methanol-ethyl-acetate-n-hexane after distilling off a solvent, and the octamethyl ester of the dimer object AH(P-Asp) 2 of a dark brown crystal (3) was obtained. (50mg, 9.8% of yield)

[0041] Example It takes each separately 50mg of P-AspMe obtained in the seven examples 1, and each is dissolved by tetrahydrofuran 10ml and 0.1ml of acetic acids, isophthalic acid dihydrazide (it is called Following mPH) and 20mg (it is called Following pPH) of terephthalic-acid dihydrazide were added to each, and it was made to react to it for two weeks under room temperature churning. After the reaction, each reaction mixture was operated like the example 6, and carried out after treatment, and the dimer object mPH(P-Asp) 2 of a dark greenish-brown crystal (4) and the octamethyl ester of pPH (P-Asp) (5)2 were obtained separately. (30mg and

30mg, 21.2% of yield, 21.2%)

[0042] Example Mn-P-Me100mg obtained in the dimerization example 2 of 8 metal complex of the same kind and Mn-P-AspMe140mg were taken separately, respectively, tetrahydrofuran 10ml and MH10mg were added to the former, tetrahydrofuran 40ml, 0.5ml of acetic acids, and AH50mg were added to the latter, and it was made to react to the bottom of room temperature churning for one week. After the reaction, in the case of the former, in the case of an example 6 and the latter, each reaction mixture was operated like the example 5, and carried out after treatment, and the octamethyl ester of the dimer complexes [AH / MH (Mn-P) (6) and / 2] 2 of a dark brown crystal (Mn-P-Asp) (7) was obtained separately. (70mg, 70mg, 26.8% of yield, 8.1%)

[0043] Example It takes each separately 50mg of methyl ester objects of (3) obtained in the of-the-same-kind metal complex-ized example 6 of nine dimers, and copper acetate and 50mg of zinc acetate were added after the dissolution and to each with the chloroform-methanol, and these were made to react to the bottom of room temperature churning for 1 hour. After the reaction (it checks in the color tone and TLC of reaction mixture), each reaction mixture was operated like the example 3, and carried out after treatment, and the octamethyl ester of the dimer complex AH(Cu-P-Asp) 2 of a dark greenish-brown crystal (8) and AH (Zn-P-Asp) (9)2 was obtained separately. (50mg, 45mg, 9.2% of yield, 7.0%)

[0044] Example 10 SUPIROGURAFISU Dimethyl ester (henceforth SP-Me), and PIROFEOHOBAIJIRU-7-aspartic acid 100mg (henceforth pyroPPB-AspMe) of dimethyl ester was taken separately, respectively, below, each was operated like the example 6, and carried out after treatment, and the tetramethyl ester of the dimer object (SP) (10) AH 2 of a brown crystal and AH (pyroPPB-Asp) (13)2 was obtained separately, respectively. (50mg, 45mg, 22.0% of yield, 16.7%)

[0045] Example Cu-P-Me200mg obtained in Mn-P-Me300mg obtained in the synthetic example 2 of 11 monomer metal complex and the example 3 was taken separately, and 10ml of MH water solutions was added to the former 6% with tetrahydrofuran 90ml, and you added 10ml of MH water solutions to the latter 2% with tetrahydrofuran 15ml, and made it react to the bottom of room temperature churning for three days. Each is operated like an example 4 below, a pyridine-ethyl-acetate-n-hexane performs reprecipitation and recrystallization, and it is monomer metal complex malonic-acid-monochrome (Mn-photograph protoporphyrin dimethyl ester) hydrazone [less or equal MH [] and the malonic-acid-monochrome (Cu-photograph protoporphyrin dimethyl ester) hydrazone

[it is called Following MH (Cu-P-Me)] which are called Mn-P-Me were obtained separately.). (250mg, 110mg, 58.7% of yield, 42.9%)

[0046] Example MH (Mn-P-Me) and 100mg each of MHs (Cu-P-Me) obtained in the synthetic example 11 of the different-species dimer in a 12 non-metal-metal complex are taken separately, and each is dissolved by tetrahydrofuran 50ml and 0.5ml of acetic acids, and P-Me150mg was added to each and it was made to react to it for three days under room temperature churning. After the reaction (it checks in TLC and UV), ethyl acetate extracted each reaction mixture, reprecipitation and recrystallization were repeated by the ethyl-acetate-n-hexane and the methanol-ethyl-acetate-n-hexane after distilling off a solvent, and the tetramethyl ester of the different-species dimer object MH (Mn-P) (P), (14), MH (Cu-P) (P), and (15) was obtained separately. (50mg, 45mg, 16.9% of yield, 15.2%)

[0047] Example Tetrahydrofuran 50ml and 10ml of acetic acids are added to the former, and tetrahydrofuran 20ml and 0.2ml of acetic acids are added to the latter, and it dissolved, 10ml of AH water solutions was dropped 20%, and you made it to take separately Cu-P-AspMe130mg obtained in Mn-P-AspMe300mg obtained in the 13 examples 2, and the example 3, respectively, and react to the bottom of room temperature churning for 2 hours. Each was operated like the example 4 below, reprecipitation and recrystallization were performed in the methanol-ethyl-acetate-n-hexane, and the adipic-acid-monochrome (Cu-photograph pro TOPORUFINIRU -6, 7-bis-aspartic-acid tetramethyl ester) hydrazone [hydrazone / monomer metal complex adipic-acid-monochrome (Mn-photograph pro TOPORUFINIRU -6, 7-bis-aspartic-acid tetramethyl ester) / each / [it is called Following AH (Mn-P-AspMe)]] [it is called Following AH (Cu-P-AspMe)] was obtained separately. (200mg, 20mg, 19.9% of yield, 4.5%)

[0048] Example Tetrahydrofuran 15ml, 0.5ml of acetic acids, and P-AspMe30mg were added to AH(Mn-P-AspMe)50mg obtained in the 14 examples 13 at tetrahydrofuran 30ml and 0.5ml of acetic acids, P-AspMe50mg, and AH(Cu-P-AspMe)20mg, and it was made to react to the bottom of room temperature churning for 24 hours. After the reaction, chloroform extracted each reaction mixture, the solvent after washing was distilled off with the physiological saline 0.9%, reprecipitation and recrystallization were repeated with methanol-ethyl-acetate-n-hexane and methanol-ethyl acetate, and the dimer object AH (Mn-P-Asp) (P-Asp) of a different kind (16) and the octamethyl ester of AH (Cu-P-Asp) (P-Asp) (17) were obtained separately. (70mg, 35mg, 15.8% of yield, 4.4%)

[0049] Example Tetrahydrofuran 100ml and 100ml of 1%AH water solutions were

added to synthetic P-Me500mg of the different-species dimer in the difference in 15 porphyrin side chain, and it was made to react to the bottom of room temperature churning for 24 hours. After the reaction, reaction mixture was rinsed, chloroform extracted, recrystallization was performed several times in the methanol-ethyl-acetate-n-hexane after distilling off a solvent, and the monomer object adipic-acid-monochrome (photograph protoporphyrin dimethyl ester) hydrazone [it is called Following AH (P-Me)] was obtained. (360mg, 57.6% of yield) Subsequently 150mg of these acquired monomer objects was dissolved in tetrahydrofuran 50ml, P-AspMe150mg and 0.2ml of acetic acids were added to this, and it was made to react to the bottom of 48-hour room temperature churning. It was operated like the example 6 below, the methanol-ethyl-acetate-n-hexane and the chloroform methanol performed reprecipitation and recrystallization after after treatment, and the hexa methyl ester of the different-species dimer object AH (P) (P-Asp) and (18) was obtained. (110mg, 20.0% of yield)

[0050] Example Tetrahydrofuran 10ml and 10ml of 10%AH water solutions were added to Mn-P-Me200mg obtained in the synthetic example 2 of 16 porphyrin side chain and the different-species dimer in the difference in a metal, and it was made to react to the bottom of room temperature churning for 24 hours. Actuation after treatment of the reaction mixture was carried out like the example 15 after the reaction, and the monomer object adipic-acid-monochrome (Mn-photograph protoporphyrin dimethyl ester) hydrazone [it is called Following AH (Mn-P-Me)] was obtained. (200mg, 67.1% of yield) Subsequently 100mg of these acquired monomer objects was dissolved in tetrahydrofuran 20ml and 0.2ml of acetic acids, P-AspMe100mg was added to this, it was operated like the example 6 below, and the hexa methyl ester of the different-species dimer object AH (Mn-P) (P-Asp) (19) was obtained after after treatment. (100mg, 33.6% of yield)

[0051] Example 2 sets of Mn-P-Me150mg obtained in the synthetic example 2 of 17 Mn-P-Me monomer derivative was taken, tetrahydrofuran 7.5ml was added to one side, and it dissolved, and the mPH water solution was dropped 10%, it dissolved in another side by tetrahydrofuran 15ml and 15ml of 50% acetic-acid water solutions, pPH750mg was added, and it was made to react to the bottom of room temperature churning separately for 1 hour, respectively. After the reaction, the former reaction mixture was operated like the example 6, carried out reprecipitation purification in the ethyl-acetate-n-hexane, and obtained monomer object isophthalic acid-monochrome (Mn-photograph protoporphyrin dimethyl ester) hydrazide [it is called Following mPH (Mn-P-Me)]. (120mg, 52.4% of yield) Reaction mixture operated another side and the

latter like the example 3, reprecipitation was repeated with methanol–tetrahydrofuran–chloroform–ethyl acetate, and monomer object terephthalic–acid–monochrome (Mn–photograph protoporphyrin dimethyl ester) hydrazide [it is called Following pPH (Mn–P–Me)] was obtained. (150mg, 65.6% of yield)

[0052] Example Monomer Mn complex mPH(Mn–p–Me) 100mg and pPH(Mn–P–Me)150mg obtained in the 18 examples 17 are taken separately, respectively, one side adds P–AspMe120mg which dissolved by tetrahydrofuran 40ml and 0.2ml of acetic acids, and was obtained in the example 1, and it dissolved by tetrahydrofuran 50ml and 0.3ml of acetic acids, and another side added P–AspMe170mg, and was made to react to the bottom of room temperature churning for 24 hours. About the former, after a reaction and reaction mixture were operated like the example 6, reprecipitation and recrystallization were repeated by the tetrahydrofuran–ethyl–acetate–n–hexane and the methanol–ethyl–acetate n–hexane after after treatment, and the hexa methyl ester of the different–species dimer object mPH (Mn–P) (P–Asp) (20) was obtained. (80mg, 21.2% of yield)

About the another side latter, it was operated like the case of the derivative of (20) of the above–mentioned after a reaction, and the hexa methyl ester of rough pPH (Mn–P) (P–Asp) was obtained. (200mg, 44.3% of yield) The acquired ester object was succeedingly given after hydrolysis and to a medium–voltage inversional layer column chromatography (octadecyl silica gel) with the conventional method in a pyridine–caustic–alkali–of–sodium water solution as it was, methanol–water (4:1) fractions were collected, the solvent was recrystallized with the pyridine–methanol after reduced pressure distilling off, and the different–species dimer object pPH (Mn–P) (P–Asp) (21) was acquired. (8.8mg, 2.1% of yield)

[0053] Example Cu–P–Me200mg obtained in the synthetic example 3 of 19 Cu–P–Me monomer derivative is taken. Tetrahydrofuran 15ml and 10ml of 10%MH water solutions are added. 24 hours, Tetrahydrofuran 15ml and 10ml of 10%AH water solutions are added to Cu–P–Me200mg. 24 hours, To Cu–P–Mel50mg, tetrahydrofuran 22ml, 15ml of methanol–water mixtures, 0.5ml of acetic acids and mPH750mg were added, tetrahydrofuran 40ml, 20ml of acetic acids, and pPHlg were added to Cu–P–Me150mg for 5 minutes, and each 4 set was made to react to the bottom of room temperature churning for 1 hour. Chloroform is added and rinsed to these [after a reaction and] 4 sets of each reaction mixture. After distilling off a solvent, It reprecipitates by the methanol–ethyl–acetate–n–hexane, the chloroform–ethyl–acetate–n–hexane, an ethyl–acetate–n–hexane, etc. It carries out by repeating recrystallization. Four sorts of monomer Cu complexes [four sorts of],

i.e., malonic-acid -, Adipic-acid -, isophthalic acid -, and below terephthalic-acid-monochrome (Cu-photograph protoporphyrin dimethyl ester) hydrazone derivative [MH (Cu-P-Me)] called AH (Cu-P-Me), mPH (Cu-P-Me), and pPH (Cu-P-Me) was obtained separately. (110mg, 160mg, 140mg and 70mg, 42.9% of yield, 59.3%, 67.5%, and 33.8%)

[0054] Example Monomer Cu complex four-sort each [MH(Cu-P-Me) 100mg obtained in the 20 examples 19, AH(Cu-P-Me) 100mg, mPH(Cu-P-Me) 100mg, and pPH(Cu-P-Me)50mg] are taken separately, respectively. To front 2 persons, tetrahydrofuran 20ml, 0.2ml of acetic acids, and P-AspMe110mg Tetrahydrofuran 40ml, 0.2ml of acetic acids, P-AspMe120mg and tetrahydrofuran 30ml, 0.2ml of acetic acids, and P-AspMe70mg were moreover dissolved in back 2 persons, and it was made to react to the bottom of room temperature 24-hour stirring. After a reaction, operate 4 sets of reaction mixture like an example 18 below, and it carries out after treatment, respectively. It reprecipitates in an ethyl-acetate-n-hexane, a chloroform-n-hexane, and a tetrahydrofuran-ethyl-acetate-n-hexane. It carried out by having repeated recrystallization and the hexa methyl ester object of four sorts of different-species dimer objects MH (Cu-P) (P-Asp) (22), AH (Cu-P) (P-Asp) (23), mPH (Cu-P) (P-Asp) (24), and pPH (Cu-P) (P-Asp) (25) was acquired. (110mg, 90mg, 30mg and 60mg, 22.7% of yield, 26.3%, 10.1%, and 42.6%)

[0055] Example MH (P-Me) (2)2 obtained in the hydrolysis example 5 of 21 dimers was hydrolyzed with caustic alkali of sodium 10% in a pyridine with the conventional method, and it stuck to the synthetic adsorbent after neutralization by the citric acid 20%, and was eluted with the methanol after rinsing. The eluate was recrystallized with methanol-ethyl acetate after vacuum concentration desiccation, and MHP2 (2) which is a dimer object of the same kind was obtained. (The yield by hydrolysis was 85.0%.)

OHP2 which hydrolysis of a dimer besides the following is operated like this, and after treatment is performed, and is a dimer object of the same kind (1), AH (P-Asp) (3)2, mPH (P-Asp) (4)2, pPH2 (P-Asp) (5), MH (Mn-P) (6)2, AH (Mn-P-Asp) (7)2, AH2 (Cu-P-Asp) (8), AH (Zn-P-Asp) (9)2, AH (SP) (10)2, AH (SP-Asp) (11)2, AH (PPB) (12)2, and AH (pyroPPB-Asp) (13)2 were obtained, respectively. (The yield by these hydrolysis was 80 - 95%.)

Moreover, MH (Mn-P) (P) a dimer of a different kind as well as the point carries out hydrolysis processing, and is [MH] a dimer object of a different kind, (14), MH (Cu-P) (P), (15), AH (P-Asp) (Mn-P-Asp) (16), AH (Cu-P-Asp) (P-Asp) (17), AH (P) (P-Asp), (18), AH (Mn-P) (P-Asp) (19), mPH (P-Asp) (Mn-P) (20), MH (Cu-P) (P-Asp) (22), AH (Cu-P) (P-Asp) (23), mPH (Cu-P) (P-Asp) (24), and pPH (Cu-P) (P-Asp) (25) were

obtained, respectively. (The yield by these hydrolysis was 80 – 95%.)

[0056] Example Laser radiation in 22 extraction organs (excitation fluorescence spectrum)

The 5mg test drug mPH (Mn-P) (P-Asp) (20) diluted with the phosphate buffer solution (1ml) to the golden hamster (one groups [five]) on 14 – the 21st which transplanted the pancreatic cancer cell of nitrosamine oncogenesis After intravenous injection, each organ which extracted each organ including cancer and was obtained -- N2-pulsed laser (N — 2,337 nm) For 2ns, 400-1000nm is irradiated, an excitation fluorescence spectrum is measured, and it is based on the peak wavelength of 470nm NADH. The wavelength of 600-900nm was examined. (N2-PLS measurement)

The result (cancer / each organ ratio) obtained like the following is shown in Table 2. Table 2 measures each excitation fluorescence spectrum of each organ extracted 6 hours after medication, and shows the value which computed the peak wavelength in 600-900nm by making peak wavelength of 470nm into criteria 1. In addition, a dimer Mn complex (for example, a compound 6 and 7) of the same kind does not have fluorescence, and N2-PLS measurement of it was not completed.

[0057]

[Table 2]

化合物名	癌	
	癌／肝	癌／肺
(3) AH(P-Asp)$_2$	3.29	3.37
(9) AH(Zn-P-Asp)$_2$	2.55	3.92
(16) AH(Mn-P-Asp) (P-Asp)	1.68	3.08
(17) AH(Cu-P-Asp) (P-Asp)	4.16	4.65
(18) AH(P) (P-Asp)	1.89	4.14
(19) AH(Mn-P) (P-Asp)	2.62	3.80
(20) mPH(Mn-P) (P-Asp)	4.00	4.17
(21) pPH(Mn-P) (P-Asp)	3.05	2.68
(24) mPH(Cu-P) (P-Asp)	6.57	4.31

[0058] Example 10micro (dansyl methionine) of evaluation substrates M of photosensitized oxidation using 23 dansyl methionine is dissolved in chloroform 1ml, 0.1micro of sensitizers M obtained in said example is added, and it is Cold under stirring. Spot It irradiated by PICL-SX (Nippon P.I.Co.Ltd) (a halogen lamp, 150W, 80,000Lux). The spot of the reaction mixture was carried out to the TLC plate (Kieselgel 60F254) for every optical exposure part, the expansion back was checked with the chloroform-methanol (3:2) and a dansyl methionine and its oxidation product (dansyl methionine sulfoxide) were checked with UV lamp (254nm). Time amount to which the dansyl methionine disappeared completely was made into reaction end time on the TLC plate, and comparison examination of the strength of the photooxidation reaction of each sensitizer was carried out. The result is shown in drawing 1 and Table 3. In addition, the axis of ordinate in drawing 1 shows Rf, an axis of abscissa shows time amount (minute), Rf value 0.79 is a dansyl methionine and 0.43 is a dansyl methionine. It is the spot of a sulfoxide. Moreover, the numeric value of Table 3 shows the completion time amount of a reaction by the part, and means that a photooxidation reaction is stronger as this value (minute) is small.

[0059]

[Table 3]

化合物名	光反応の強さ
MHP	2
PhotofrinII®	10<
(2) MHP_2	2
(3) $AH(P-Asp)_2$	2
(4) $mPH(P-Asp)_2$	3
(5) $pPH(P-Asp)_2$	3
(9) $AH(Zn-P-Asp)_2$	3
(14) MH (Mn-P) (P)	-
(16) AH (Mn-P-Asp) (P-Asp)	-
(17) AH (Cu-P-Asp) (P-Asp)	10<
(20) mPH (Mn-P) (P-Asp)	-
(22) MH (Cu-P) (P-Asp)	10<
(24) mPH (Cu-P) (P-Asp)	10<

[0060] Example The mass of this derivative was measured according to 24 mass-analysis FAB mass spectrometry. As an example of representation of the measurement result, the FAB mass analysis spectrum of the methyl ester object of MHP2 (2), MH (Mn-P) (6)2, AH (Mn-P-Asp) (P-Asp) (16), and AH (Cu-P-Asp) (P-Asp) (17) is shown in drawing 2 , drawing 3 , drawing 4 , and drawing 5 .

[0061] Example 25 ultraviolet-absorption analysis of a spectrum (albumin test)

It is known that a porphyrin compound will form two monomers or a polymer in an albumin solution. This property is a seal or ** by migration of an absorption maximum value or fluctuation of an absorbancy index being seen by analyzing by changing various albumin concentration. Therefore, it is an easy screening test for examining compatibility with a cancer cell. Albumin 54mg is dissolved in a 3ml physiological saline, and it considers as concentration 1.8%. Subsequently, the liquid which diluted this 10 times and was made into 0.18% was diluted with the common ratio 3, and the liquid of each albumin concentration (1.8, 0.18, 0.06, 0.02, 0.0066, 0.0022%) was prepared. On the other hand, 1mg of porphyrin derivatives was dissolved in 1ml (pH8.0) of

phosphate buffer solutions, and it was made 100ml with the physiological saline. And 2ml of albumin diluents and 2ml of porphyrin solutions were mixed, the albumin last concentration of mixture was made into 0.9, 0.09, 0.03, 0.01, 0.0033, and 0.0011%, and ultraviolet absorption spectrum measurement (350-900nm) was performed. Moreover, it measured similarly in the physiological saline and the methanol solution instead of the albumin diluent. These measurement results are shown in Table 4. As the example of representation, the ultraviolet absorption spectrum of AH (P) (P-Asp) and (18) is shown in drawing 6 and drawing 7.

[0062]

[Table 4]

化合物名	波長 (nm)		
	生理食塩水	メタノール	0.9 %アルブミン
(3) AH(P-Asp)$_2$	677	675	678
(7) AH(Mn-P-Asp)$_2$	682	676	679
(9) AH(Zn-P-Asp)$_2$	653	653	655
(16) AH(Mn-P-Asp) (P-Asp)	677	676	678
(17) AH(Cu-P-Asp) (P-Asp)	677	677	678
(18) AH(P) (P-Asp)	681	679	683
(19) AH(Mn-P) (P-Asp)	677	676	679
(20) mPH(Mn-P) (P-Asp)	678	674	680
(22) MH(Cu-P) (P-Asp)	674	673	676
(23) AH(Cu-P) (P-Asp)	674	673	673
(24) pPH(Cu-P) (P-Asp)	674	673	677

[0063]

[Effect of the Invention] Since the porphyrin derivative with this invention has the accumulation nature to a cancer cell, the reactivity over external energy, and a

destructive operation of a cancer cell, and a certain derivative has non-phosphorescence or non-phosphorescence non-fluorescence, toxicity moreover is not discovered to a normal cell and a compound can respond according to the purpose, it reaches [as cancer treatment medicine or a cancer diagnostic drug] to an extreme and is useful.

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] It is drawing showing the thin-layer chromatogram using AH(P-Asp)2(3) octamethyl ester as a sensitizer.

[Drawing 2] It is drawing showing the mass analysis spectrum (FAB-NBA) of MHP2(2) tetramethyl ester (C75H80N 12O12, 1340.6).

[Drawing 3] It is drawing showing the mass analysis spectrum (FAB-NBA) of MH(Mn-P)2(6) tetramethyl ester (C75H82N12O16Mn2, 1516.4).

[Drawing 4] It is drawing showing the mass analysis spectrum (FAB-NBA) of AH(Mn-P-Asp) (P-Asp)(16) octamethyl ester (C98H115N16O26Mn, 1986.8).

[Drawing 5] It is drawing showing the mass analysis spectrum (FAB-NBA) of AH(Cu-P-Asp) (P-Asp)(17) octamethyl ester (C98H112N16O24Cu, 1959.7).

[Drawing 6] It is drawing showing the ultraviolet absorption spectrum of AH (P) (P-Asp) and (18).

[Drawing 7] It is drawing showing the ultraviolet absorption spectrum of AH (P) (P-Asp) and (18).

[Description of Notations]

1 Porphyrin Solution and Mixture of Physiological Saline
(0% of albumin concentration)

2 Mixture of Porphyrin Solution and Albumin Solution
(0.0011% of albumin concentration)

3 Mixture of Porphyrin Solution and ARUPUMIN Solution
(0.0033% of albumin concentration)

4 Mixture of Porphyrin Solution and Albumin Solution
(0.01% of albumin concentration)

5 Mixture of Porphyrin Solution and Albumin Solution
(0.03% of albumin concentration)

6 Mixture of Porphyrin Solution and Albumin Solution
(0.09% of albumin concentration)

7 Mixture of Porphyrin Solution and Albumin Solution
(0.9% of albumin concentration)
8 Porphyrin Solution and Mixture of Methanol

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(54)【発明の名称】　ポルフィリン二量体とその用途

(57)【要約】

【目的】　本発明は、特定の臓器特に癌への親和性に優れ、正常組織からの排出速度が速く光毒性を低減させることができ、かつ金属錯体の金属を変換することにより燐光蛍光性［光化学治療（ＰＤＤＴ）用］、無燐光蛍光性［蛍光診断（ＰＤＤＴ）用］および無燐光無蛍光性［核磁気共鳴診断（ＭＲＩ）用］を持つ用途に応じたポルフィリン二量体を合成・探索し、ＰＤＤＴならびにＭＲＩに適した薬剤を提供することを目的とする。

【構成】　本発明は、アルデヒド基またはケトン基担持ポルフィリン類にビスヒドラゾン（スペーサー）を介して得られたポルフィリン二量体とその金属錯体で構成される。

1

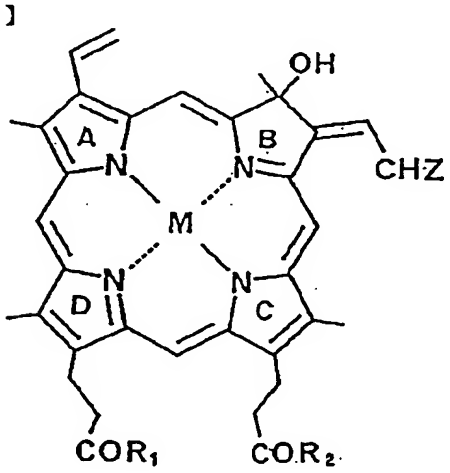
【特許請求の範囲】

【請求項１】　一般式　（Ｉ）　化１

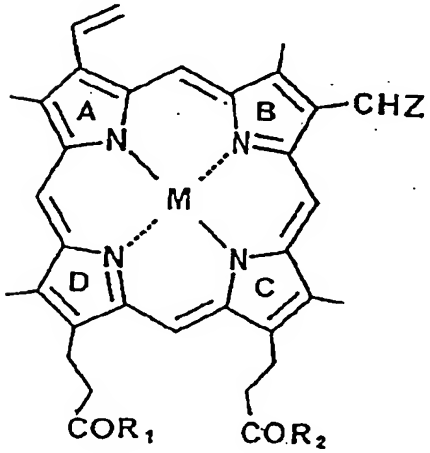
［式中、Ａは（ＣＨ２）ｎまたはフェニレン基、ｎは０～８、Ｘ、Ｙは化２、化３または化４で示すポルフィリンあるいは金属ポルフィリン（但し式中、Ｒ１、Ｒ２はそれぞれＯＨまたはアミノ酸から水素を除いた残基、Ｒ３はＨまたはＣＯＯＣＨ３、Ｍは２Ｈ、Ｍｎ、ＣｕまたはＺｎを示す）側鎖のケトンまたはアルデヒドから酸素を除いた残基］で示されるポルフィリン二量体またはそれらの金属錯体。（但し式中、ポルフィリン骨格側鎖のＺは化１との結合部位を示す。またポルフィリン骨格の４つのピロール環のうちＡ及びＢ環の側鎖の官能基がそれぞれ入れ替わった位置異性体も含む。）

【化１】

【化２】

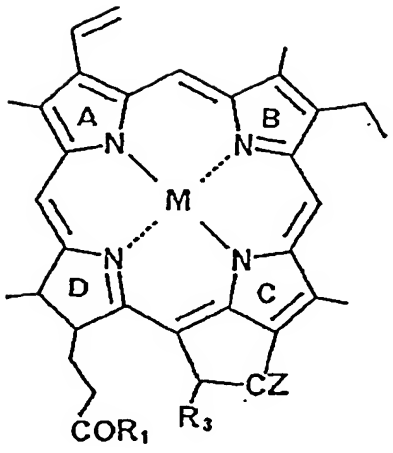


【化３】



【化４】

2



【請求項２】　請求項１記載のポルフィリンおよび金属ポルフィリン化合物からなる光物理化学的診断用および／または治療用増感剤。

【請求項３】　癌の診断および／または治療に使用される請求項２記載の光物理化学用増感剤。

【請求項４】　請求項１記載のＭｎ金属ポルフィリン化合物からなる核磁気共鳴用造影剤。

【請求項５】　癌のイメージングに使用される請求項４記載の核磁気共鳴用診断剤。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は、ポルフィリン二量体とその用途、特に新規なポルフィリン（無金属錯体一無金属錯体化合物）および金属ポルフィリン（金属錯体一金属錯体化合物）二量体ならびにポルフィリン一金属ポルフィリン（無金属錯体一金属錯体化合物）誘導体を有効成分とする光物理化学的診断用および治療用の増感剤ならびに核磁気共鳴用造影剤および／または光物理化学による癌の診断および治療ならびに核磁気共鳴による診断に用いる薬剤に関する。

【０００２】

【従来の技術】癌の新しい診断・治療法として光物理化学的蛍光診断・治療［Ｐｈｏｔｏｄｙｎａｍｉｃ　Ｄｉａｇｎｏｓｉｓ　ａｎｄ　Ｔｈｅｒａｐｙ（ＰＤＤＴ）］が行われている。これはある種のポルフィリン化合物を静脈注射などの方法により投与し、癌組織に保持させた後、レーザー光を照射して癌組織のみを選択的に蛍光診断し破壊するというものである。ＰＤＤＴは、ポルフィリンの癌組織に保持される時間が正常組織に比べて長いという性質と光増感作用を持つという２つの性質を利用している。過去１３年間に世界中で３０００人以上の人々がＰＤＤＴによる悪性腫瘍の治療を受けており、癌治療法の１つとして定着しつつある。ＰＤＤＴにより良好な治療成績が報告されている癌種は、網膜癌、皮膚癌、食道癌、表在性膀胱癌、初期の肺癌など多岐に渡っている。また最近は、内視鏡を用いた蛍光診断にも

利用されるようになった。

【０００３】現在ＰＤＤＴに使用されている薬剤は主としてヘマトポルフィリン誘導体（ＨＰＤ）およびそのエーテル体および／またはエステル体の二量体である。ＨＰＤはヘマトポルフィリンを酢酸中硫酸処理し、さらに０．１Ｎ水酸化ナトリウムで処理して得られる混合物である。二量体はＨＰＤの疎水性の高い成分を主として含んでおり、ＨＰＤとともに複雑な混合物であり活性成分が不明である。また成分比が一定でないために治療効果が極めて不安定である。

【０００４】一方、ＰＤＤＴのための新しいポルフィリン誘導体として、ポルフィリン二量体をＤｏｕｇｈｅｒｔｙらが米国特許４６４９１５１号（１９８７）に、ＫｅｓｓｅｌらがＰｈｏｔｏｃｈｅｍ．Ｐｈｏｔｏｂｉｏｌ．，５３，４７５（１９９１）に、Ｐａｎｄｅｙらが Ｔｅｔｒａｈｅｄｒｏｎ Ｌｅｔｔ．，２９，４６５７（１９８８）に、ＣｏｌｌｍａｎらがＪ．Ａ．Ｃ．Ｓ．，１０５，２６９９（１９８３）に開示している。我々も種々検討し、Ａｇｒｉｃ．Ｂｉｏｌ．Ｃｈｅｍ．，５５，２４４１（１９９１）に開示してきた。しかしながら、ＰＤＤＴ用の増感剤として用いるには上記化合物では合成、安定性、水溶性、無光毒性の面において実用化が困難であった。

【０００５】またＰＤＤＴに使われるレーザー光の組織透過性の問題もある。ＨＰＤやその二量体は最大吸収波長が６３０ｎｍであり、モル吸光係数も３０００と低い。６３０ｎｍの光では組織透過性が悪く、ＰＤＤＴの治療効果が５～１０ｍｍの表層癌に限定されてしまっている。

【０００６】一方レーザー装置の方にも問題がある。現在最もよく使用されている色素レーザーは安定性が悪く、運用上取扱いが難しい。最近注目を集めているチタンサファイアレーザーを用いれば運用がかなり簡単になる。しかしこのレーザーを用いると６７０ｎｍ以上６００ｎｍ以下の吸収波長に限られ、６３０ｎｍ付近の吸収波長を持つＨＰＤやその二量体に適用できない。

【０００７】更に薬剤の副作用として一時的な光過敏症を引き起こすことが知られている。このため薬剤投与後、皮膚などの正常組織が光増感作用で破壊されないように患者を長期間暗所に閉じ込めておかなければならない。ＨＰＤおよびその二量体は正常組織からの排出速度が遅いので長いときには６週間以上も光過敏症が残ることもある。現在使用されている薬剤はこうした多くの問題点を抱えておりＨＰＤおよびその二量体に代わる新しい薬剤の開発が強く望まれている。そこで上記薬剤が持つ欠点を克服するものとして単一化合物でありかつより長波長領域（６５０～８００ｎｍ）に吸収を持つ化合物が第２世代の薬物として提案されている。現在フタロシアニンなどのアザポルフィリン類、クロリン・バクテリオクロリンなどのポルフィリン類、テキサフィリンなどの環拡張型ポルフィリン類などさまざまな化合物がＨＰＤやその二量体に代わる薬剤として研究されている。また、癌の治療用だけでなく蛍光診断用として前記ＨＰＤおよびその二量体が双方の薬剤として併用されている。しかし本来ならばその薬剤が持つ光毒性が故に治療用と診断用は分離されるべきであって、無光毒性（無燐光性）蛍光診断剤が強く望まれていた。

【０００８】

【発明が解決しようとする課題】本発明者らは、単一成分であり安定かつ癌組織に対する良好な集積性を維持したまま、正常組織からは排出速度が速く、蛍光診断剤として適用する場合には無光毒性であり（蛍光寿命が長く、燐光寿命が短い化合物が範疇にはいる）、しかもできうればチタンサファイアレーザー（６７０ｎｍ以上６００ｎｍ以下の波長）の使用が可能であるポルフィリン誘導体を探索し、ＰＤＤＴに適した光増感剤を提供することを目的として、種々の研究を重ねた。

【０００９】

【問題を解決するための手段】その結果、前願誘導体（特願平３－３２３５９７号）の中で血液由来のプロトポルフィリンより合成誘導体化して得られたクロリン類または葉緑素由来のフェオホーバイド類をある種のスペーサーを介して二量体にすると、単一成分で、癌組織に対して優れた集積性と正常組織より良好な排出性を、しかも６７０ｎｍ以上の吸収波長を持ち、かつ良好なＰＤＤＴ効果を有することを見出した。更にこれらの反応を組み合わせることにより無金属錯体ー無金属錯体化合物、金属錯体ー金属錯体化合物ならびに無金属錯体ー金属錯体化合物の二量体の合成にも成功した。なかでも、無金属錯体ー金属錯体二量体のある種の半金属化合物は無光毒性（無燐光性）蛍光の性質が存在していた。

【００１０】また本発明者らは前願誘導体と同様に、これら二量体とアルブミンの混液の紫外線吸収（ＵＶ）スペクトルを分析したところ、スペクトルの動向が正の方向すなわち特定臓器特に癌への親和性につながっていることが分かった。

【００１１】一方、本発明者らは本研究開発途中で、ダンシルメチオニン基質の系を用いる光増感酸化反応の評価方法を見出した。この方法を用いれば、薄層クロマトグラフィー（ＴＬＣ）や高速液体クロマトグラフィー（ＨＰＬＣ）により二量体における光に対する反応性の有無ならびに強弱を簡便に評価できた。なお、この評価法による値は燐光寿命の長短と良い相関関係を示していた。

【００１２】他方、以前の出願明細書（特開平２－１３８２８０号）の中でも述べているように蛍光強度の測定を行えば種々の特性が物理化学的に証明できる。したがって、蛍光を持つポルフィリンに燐光寿命がないかまたは短い金属ポルフィリンを結合せしめると無光毒性蛍光診断剤が誕生すると思われた。その測定結果の主なもの

を表１に示す。以上を考え合わせると、本発明の二量体の中でも無金属錯体ー無金属錯体化合物は治療用に、金属錯体ー金属錯体化合物は治療用または核磁気共鳴診断（ＭＲＩ）用に、無金属錯体ー金属錯体化合物は蛍光診

断用の薬剤として用途別に利用できることが判かった。

【００１３】

【表１】

化　合　物　名	相対蛍光強度
ＭＨＰ	２０００
Ｐｈｏｔｏｆｒｉｎ Ⅱ®	２００
(2) ＭＨＰ$_2$	６００
(3) ＡＨ（Ｐ－Ａｓｐ）$_2$	５６０
(4) ｍＰＨ（Ｐ－Ａｓｐ）$_2$	８００
(5) ｐＰＨ（Ｐ－Ａｓｐ）$_2$	６５０
(6) ＭＨ（Ｍｎ－Ｐ）$_2$	０
(14) ＭＨ（Ｍｎ－Ｐ）（Ｐ）	４０
(16) ＡＨ（Ｍｎ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）	６０
(17) ＡＨ（Ｃｕ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）	５０
(20) ｍＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）	４５
(22) ＭＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）	１２
(24) ｍＰＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）	７０

【００１４】本発明は上記の知見に基づいて完成されたものであって、その要旨は

一般式　（Ｉ）　化５

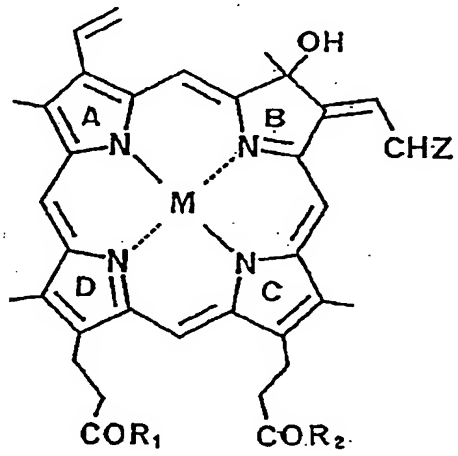
［式中、Ａは（ＣＨ$_2$）$_n$またはフェニレン基、ｎは０～８、Ｘ、Ｙは化６、化７または化８で示すポルフィリンあるいは金属ポルフィリン（但し式中、Ｒ$_1$、Ｒ$_2$はそれぞれＯＨまたはアミノ酸から水素を除いた残基、Ｒ$_3$はＨまたはＣＯＯＣＨ$_3$，Ｍは２Ｈ、Ｍｎ、ＣｕまたはＺｎを示す）側鎖のケトンまたはアルデヒドから酸素を除いた残基］で示されるポルフィリン二量体またはそれらの金属錯体。（但し式中、ポルフィリン骨格側鎖のＺは化１との結合部位を示す。またポルフィリン骨格の４つのピロール環のうちＡ及びＢ環の側鎖の官能基がそれぞれ入れ替わった位置異性体も含む。）

【００１５】

【化５】

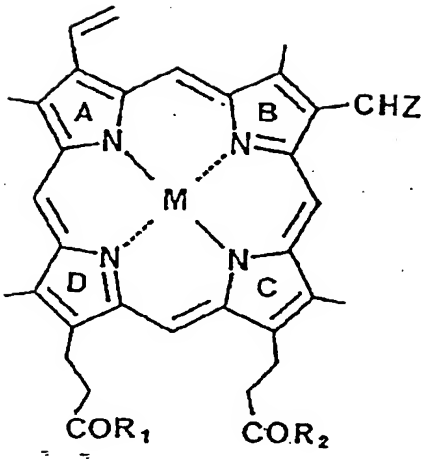
【００１６】

【化６】



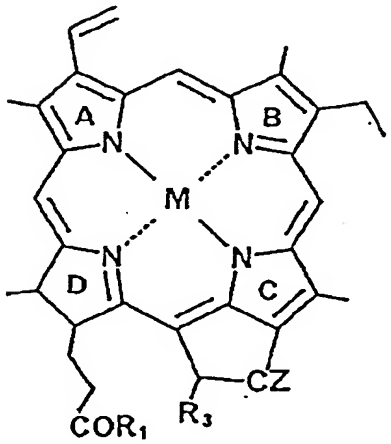
【００１７】

【化７】



【００１８】

【化８】



【００１９】上記各記号の意味に関して使用された「アミノ酸」なる語は必須アミノ酸、「フェニレン基」なる語はメタ、パラ位結合部位を意味する。

【００２０】本発明の各種ポルフィリン二量体は、自体常套によって製造することができる。一般式（Ｉ）に対応するＸとＹが同種のポルフィリン二量体（無金属錯体一無金属錯体化合物）にあっては、Ｒ１、Ｒ２またはＲ３を有するものを構成し（工程ａ）、ついで次の工程ｂに進みスペーサーを介して一段階に同種の二量体と成し、得られたポルフィリン二量体を加水分解せしめる（工程ｃ）。また必ずしも工程（ａ）、（ｂ）、（ｃ）と順次反応せしめる必要もなく、例えば工程（ｂ）、（ａ）、（ｃ）または工程（ａ）、（ｃ）、（ｂ）のように工程順が代わってもよい。なお、後で述べる様にＸとＹが同種の二量体を工程（ｅ）を経る二段階で合成してもよい。

【００２１】一方、一般式（Ｉ）に対応するＸとＹが同種の金属ポルフィリン二量体（金属錯体一金属錯体化合物）にあっては、まずＭを有するものを構成し（工程ｄ）、ついでこれを前述と同様にして誘導体化し、工程

（ａ）、（ｂ）、（ｃ）と順次反応せしめる。また必ずしも工程順が一定でなくても先で述べたように工程順が変わってもよい。

【００２２】他方、一般式（Ｉ）に対応するＸとＹが異種のポルフィリン一金属ポルフィリン二量体（無金属錯体一金属錯体化合物）にあっては、まずＭを有するものを構成し（工程ｄ）、別途にＲ１、Ｒ２およびＲ３を有するポルフィリンを構成する（工程ａ）。その後、工程ｄあるいは工程ａで得られたポルフィリン誘導体のうちどちらか一方にスペーサーを結合せしめ（工程ｅ）。ついで、工程ａまたは工程ｄから得られたポルフィリン化合物を反応せしめて二段階で異種ポルフィリン二量体を得、以下工程ｃへと進む。また、ポルフィリン側鎖の違いによる異種ポルフィリン二量体（無金属錯体一無金属錯体化合物）もＭを有するものを構成する以外はこれと同様にして二段階で合成する。

【００２３】構成工程（ａおよびｄ）はＪ．Ｅ．Ｆａｌｋ著［Ｐｏｒｐｈｙｒｉｎｓ　ａｎｄ　Ｍｅｔａｌｌｏｐｏｒｐｈｙｒｉｎｓ］（Ｅｌｓｅｖｉｅｒ発行、１９７５年）およびＤ．Ｄｏｌｐｈｉｎ著［Ｔｈｅ　Ｐｏｒｐｈｙｒｉｎｓ］（Ａｃａｄｅｍｉｃ　Ｐｒｅｓｓ発行、１９７８年）等に記載された常套の方法によってこれを行うことができる。

【００２４】例えば（Ｉ）に対応するＲ１、Ｒ２およびＲ３を有するポルフィリン化合物およびそれらの金属錯体であるものは、特開昭６１－７２７９号、特開昭６１－８３１８５号、特許公報昭６３－１３９９７号、特開平２－７６８８１号、特開平２－１３８２８０号，特開平４－５９７７９号および特願平３－３２３５９７号に記載された方法に従ってこれを調製すれば良い。すなわち工程（ａ）については光化学反応を利用してクロリン化工程（フォトプロトポルフィリン）を経由し、アミノ酸残基の結合工程に付してこれを行うことができる。工程（ｄ）については通常、金属の塩化物、酢酸塩、硫酸塩、硝酸塩等を使用してこれを行う。金属の種類としては、長燐光寿命効果があるＺｎ、逆に短縮効果があるＭｎ、Ｃｕ、Ｆｅなどが挙げられる。またこの金属導入工程（ｄ）は（ａ）または（ｂ）工程の前後を問わず、必要に応じ調製して良い。人為的に合成する代わりに、植物や動物のような天然資源からこれを採取してもよい。

【００２５】次に、以上のようにして構成したクロリン化合物および／またはその錯体、ならびにフェオホーバイド化合物を縮合工程（ｂ）または（ｃ）に付す。すなわちプロトポルフィリン　ジメチルエステル（以下ＰＰ－Ｍｅと言う）を光化学反応処理して得られた１－ヒドロキシー２－ホルミルエチリデンープロトポルフィリン　ジメチルエステル（以下フォトプロトポルフィリン　ジメチルエステル、Ｐ－Ｍｅと言う）および／またはその錯体、ならびに緑葉天然物から単離精製したフェオホーバイド誘導体にジカルボン酸ビスヒドラジド誘導体を

反応させて目的の縮合体ポルフィリン化合物を製造する。このものは一般有機化学実験書中［ヒドラゾンとケトンまたはアルデヒド化合物との付加または縮合反応］に記載された常套の方法によってこれを行うことができる。なお、いずれの場合も適宜脱水剤や脱酸剤のような反応促進剤や縮合剤の使用も考慮されてよい。

【００２６】以下、代表例を挙げてポルフィリン二量体化合物（Ｉ）の調製を更に具体的に説明する。例えばＸとＹが同種のポルフィリン二量体（すなわち無金属錯体－無金属錯体化合物ならびに金属錯体－金属錯体化合物）の場合には、ケトンまたはアルデヒド担持ポルフィリン誘導体またはその金属錯体にジカルボン酸ビスヒドラジド（例えば修酸ジヒドラジド、マロン酸ジヒドラジド、アジピン酸ジヒドラジド、イソフタル酸ジヒドラジド、テレフタル酸ジヒドラジド等）をＴＨＦなどの溶媒中で適宜縮合剤（例えば酸、アルカリ等）を用いて反応せしめて、これらビスヒドラゾンをスペーサーとした同種のポルフィリン二量体（Ｉ）を一段階で得る。その具体例としては以下のものを挙げることができる。

【００２７】（１）修酸－ビス（フォトプロトポルフィリン）ヒドラゾン（以下ＯＨＰ$_2$と言う）

（２）マロン酸－ビス（フォトプロトポルフィリン）ヒドラゾン（以下ＭＨＰ$_2$と言う）

（３）アジピン酸－ビス（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｐ－Ａｓｐ）$_2$と言う］

（４）イソフタル酸－ビス（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ｍＰＨ（Ｐ－Ａｓｐ）$_2$と言う］

（５）テレフタル酸－ビス（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ｐＰＨ（Ｐ－Ａｓｐ）$_2$と言う］

（６）マロン酸－ビス（Ｍｎ－フォトプロトポルフィリン）ヒドラゾン［以下ＭＨ（Ｍｎ－Ｐ）$_2$と言う］

（７）アジピン酸－ビス（Ｍｎ－フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｍｎ－Ｐ－Ａｓｐ）$_2$と言う］

（８）アジピン酸－ビス（Ｃｕ－フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｃｕ－Ｐ－Ａｓｐ）$_2$と言う］

（９）アジピン酸－ビス（Ｚｎ－フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｚｎ－Ｐ－Ａｓｐ）$_2$と言う］

（１０）アジピン酸－ビス（スピログラフィス）ヒドラゾン［以下ＡＨ（ＳＰ）$_2$と言う］

（１１）アジピン酸－ビス（スピログラフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（ＳＰ－Ａｓｐ）$_2$と言う］

（１２）アジピン酸－ビス（フェオホーバイド）ヒドラゾン［以下ＡＨ（ＰＰＢ）$_2$と言う］

（１３）アジピン酸－ビス（ピロフェオホーバイジル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（ｐｙｒｏＰＰＢ－Ａｓｐ）$_2$と言う］

【００２８】一方、ＸとＹが異種のポルフィリン二量体（すなわち無金属錯体－金属錯体化合物、同一の無金属または金属錯体のポルフィリン二量体であってもＸとＹが異なる化合物）の場合には、まずケトンあるいはアルデヒド担持化合物またはそれらの金属錯体を前記ジカルボン酸ビスヒドラジドにて溶媒中で適宜縮合剤を用いて反応せしめ、ＸまたはＹどちらかが結合したモノヒドラゾン体を得る。ついで、得られたモノ体にケトンあるいはアルデヒド担持化合物またはそれらの金属錯体を前述と同様に反応せしめて、異種のポルフィリン二量体（Ｉ）を得る。その具体例としては以下のものを挙げることができる。

【００２９】（１４）マロン酸－モノ（Ｍｎ－フォトプロトポルフィリン）－モノ（フォトプロトポルフィリン）ヒドラゾン［以下ＭＨ（Ｍｎ－Ｐ）（Ｐ）と言う］

（１５）マロン酸－モノ（Ｃｕ－フォトプロトポルフィリン）－モノ（フォトプロトポルフィリン）ヒドラゾン［以下ＭＨ（Ｃｕ－Ｐ）（Ｐ）と言う］

（１６）アジピン酸－モノ（Ｍｎ－フォトプロトポルフィニル－６、７－ビスアスパラギン酸）－モノ（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｍｎ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）と言う］

（１７）アジピン酸－モノ（Ｃｕ－フォトプロトポルフィニル－６、７－ビスアスパラギン酸）－モノ（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｃｕ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）と言う］

（１８）アジピン酸－モノ（フォトプロトポルフィリン）－モノ（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｐ）（Ｐ－Ａｓｐ）と言う］

（１９）アジピン酸－モノ（Ｍｎ－フォトプロトポルフィリン）－モノ（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）と言う］

（２０）イソフタル酸－モノ（Ｍｎ－フォトプロトポルフィリン）－モノ（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ｍＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）と言う］

（２１）テレフタル酸－モノ（Ｍｎ－フォトプロトポルフィリン）－モノ（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ｐＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）と言う］

（２２）マロン酸－モノ（Ｃｕ－フォトプロトポルフィリン）－モノ（フォトプロトポルフィニル－６、７－ビスアスパラギン酸）ヒドラゾン［以下ＭＨ（Ｃｕ－Ｐ）

（Ｐ－Ａｓｐ）と言う]
（２３）アジピン酸ーモノ（Ｃｕーフォトプロトポルフィリン）ーモノ（フォトプロトポルフィニルー６、７ービスアスパラギン酸）ヒドラゾン［以下ＡＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）と言う]
（２４）イソフタル酸ーモノ（Ｃｕーフォトプロトポルフィリン）ーモノ（フォトプロトポルフィニルー６、７ービスアスパラギン酸）ヒドラゾン［以下ｍＰＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）と言う]
（２５）テレフタル酸ーモノ（Ｃｕーフォトプロトポルフィリン）ーモノ（フォトプロトポルフィニルー６、７ービスアスパラギン酸）ヒドラゾン［以下ｐＰＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）と言う]
【００３０】本発明によるポルフィリン誘導体の医薬品製剤の製造は自体公知法により行われ、本発明による誘導体を適当な緩衝液で溶解するだけでよい。好適な添加物として例えば医薬的に認容できる溶解補助剤（例えば有機溶媒）、ｐＨ調製剤（例えば酸、塩基、緩衝液）、安定剤（例えばアスコルビン酸）、賦形剤（例えばグルコース）、等張化剤（例えば塩化ナトリウム）などが配合されても良い。
【００３１】本発明による薬剤はＰＤＤＴ用薬剤としての必要充分な特性すなわち長燐光寿命場合によっては短燐光寿命、無燐光蛍光性（蛍光のみで光反応がない）、アルブミンに対する親和性、特定臓器特に癌に対する特異的集積性、光反応性、光殺細胞効果、吸収波長、水溶性、純度などを充分満足しているものである。本発明による薬剤の良好な水溶性は、高濃度溶液（５０ｍｇ／ｍｌ）の製造を可能とした。一般に、ＰＤＤＴ用薬剤として適用するためには本発明の薬剤を１ｍｇ～５ｍｇ／ｋｇ体重の量、ＭＲＩ用薬剤としては１ｍｇ～１０ｍｇ／ｋｇ体重の量で投与するのが望ましい。
【００３２】
【作用】本発明にかかるポルフィリン二量体とその金属錯体は、ポルフィリン骨格側鎖のケトンおよび／またはアルデヒド残基にスペーサーとしてビスヒドラゾン誘導体を用いた点に化学構造上の特徴を有し、その結果種々の生理学的もしくは薬理学的特性を発揮する。
【００３３】これらポルフィリン誘導体は癌細胞に選択的に集積し、かつ癌細胞からの排泄が遅い。なお、正常な臓器や細胞からは速やかに排泄されるため、それらに損傷を与えることはない。元来、ポルフィリン誘導体の殆んどのものは光に対して強い作用を有するが、本発明に従ってポルフィリン誘導体を二量体化することによって正常組織からの排泄性を高めるとともに、光毒性の発現を極力抑制するようデザインした誘導体が可能となった。また、クロリン誘導体を利用することによって波長がレッドシフトするので治療効果の深達度をはかることができた。これらの特性（癌親和性、無燐光蛍光性、無光毒性、光殺細胞効果、吸収波長、水溶性）に基づき、本発明のポルフィリン二量体とその金属錯体は特定の臓器、特に癌や悪性腫瘍に対するＰＤＤＴ用またはＭＲＩ用薬剤として有用である。
【００３４】以下実施例を挙げて説明する。なお、実施例での収率はすべて出発原料であるＰ－Ｍｅやフェオホーバイド（以下ＰＰＢと言う）から換算して求めた値である。
【００３５】
【実施例】
実施例　１
ポルフィリンのアスパラギン酸誘導体化
特開平２－１３８２８０号および特開平４－５９７７９号に掲げた方法により合成したＰ－Ｍｅ２ｇを用い、これにピリジン５０ｍｌを加え溶解後、１０％苛性ソーダにて常法により加水分解した。加水分解液を２０％クエン酸水溶液にて中和後クロロホルムで抽出した。抽出物を減圧濃縮し、酢酸エチルーｎーヘキサンにより再沈殿後、フォトプロトポルフィリン（以下Ｐと言う）１．７５ｇを得た。（エステルのケン化）
得られたＰの全量をテトラヒドロフランに溶解しジシクロヘキシルアミン（ＤＣＨＡ）にて常法によりＰ－ＤＣＨＡ塩（２．０ｇ）とした。本ＤＣＨＡ塩をクロロホルム１５０ｍｌに溶解し、アスパラギン酸　ジメチルエステル（ＡｓｐＭｅ）塩酸塩２ｇを加え、撹拌下に水溶性カルボジイミド（ＷＳＣ）２ｇを徐々に加えて１．５時間反応せしめた。反応後（ＴＬＣにて反応終末点を確認）、反応液を水洗分液後、クロロホルム層を減圧濃縮した。得られた濃縮物を酢酸エチルーエーテルーｎーヘキサンにて再沈殿および再結晶化を繰り返し行い、暗緑色結晶のフォトプロトポルフィニルー６、７ービスアスパラギン酸　テトラメチルエステル（以下Ｐ－ＡｓｐＭｅと言う）を得た。（１．２ｇ、収率４２．４％）
【００３６】実施例　２
ポルフィリン化合物のＭｎ金属錯体化
特開平２－１３８２８０号および特開平４－５９７７９号に掲げた方法を改良して合成した。Ｐ－Ｍｅ３ｇおよび実施例１で得られたＰ－ＡｓｐＭｅ１００ｍｇをそれぞれ酢酸に溶解し、酢酸マンガンを加えて５０℃に加温し、撹拌下２時間反応させた。反応後、反応液に０．９％生理食塩水を加え沈殿物を別々に得た。得られた沈殿物を水洗乾燥後、メタノールー酢酸エチルーｎーヘキサンにより再沈殿を繰り返し、暗褐色結晶のＭｎーフォトプロトポルフィリン　ジメチルエステル（以下Ｍｎ－Ｐ－Ｍｅと言う）およびＭｎーフォトポルフィニルー６、７ービスアスパラギン酸　テトラメチルエステル（以下Ｍｎ－Ｐ－ＡｓｐＭｅと言う）を別々に得た。（２．８ｇおよび９０ｍｇ、収率８１．８％および３４．７％）
【００３７】実施例　３
ポルフィリン化合物のＣｕ金属錯体化
特開平２－１３８２８０号および実施例１に掲げた方法

を改良して合成した。Ｐ－Ｍｅｌｇおよび実施例１で得られたＰ－ＡｓｐＭｅ１５０ｍｇをそれぞれ別々にクロロホルム－メタノール（２：１ｖ／ｖ）に溶解し、酢酸銅を加えて室温で撹拌下３０分間反応させた。反応後（鮮緑色）、それぞれの反応液にクロロホルムを加え０．９％生理食塩水で洗浄し、クロロホルム層を減圧濃縮した。得られた残渣を酢酸エチル－ｎ－ヘキサンにて再沈殿を繰り返し、暗緑色結晶のＣｕ－フォトプロトポルフィリン　ジメチルエステル（以下Ｃｕ－Ｐ－Ｍｅと言う）およびＣｕ－フォトポルフィニル－６、７－ビスアスパラギン酸　テトラメチルエステル（以下Ｃｕ－Ｐ－ＡｓｐＭｅと言う）を別々に得た。（１ｇおよび１３０ｍｇ、収率９１．０％および３４．４％）

【００３８】実施例　４

モノマー体の合成

Ｐ－Ｍｅ５００ｍｇにテトラヒドロフラン１５０ｍｌを加え、室温撹拌下に１％マロン酸ジヒドラジド（以下ＭＨと言う）水溶液５０ｍｌを滴下し２４時間反応させた。反応後（ＴＬＣにてＲｆ値の移動を確認）、反応液を酢酸エチルにて抽出し、水洗乾燥減圧濃縮した。得られた濃縮物（４００ｍｇ）をシリカゲルカラムクロマトグラフィーに付し、酢酸エチル－メタノール（９：１）および（１：１）溶出画分を集め溶媒を留去した。それぞれの残渣を酢酸エチル－ｎ－ヘキサンにより再結晶化し、黒褐色結晶のダイマー体ＭＨＰ$_2$（２）のテトラメチルエステルおよびモノマー体マロン酸－モノ（フォトプロトポルフィリン　ジメチルエステル）ヒドラゾン［以下ＭＨ（Ｐ－Ｍｅ）と言う］を別々に得た。（５０ｍｇおよび１２０ｍｇ、収率４．６％および２０．３％）

【００３９】実施例　５

二段階法による同種二量体の合成

実施例４で得られたＭＨ（Ｐ－Ｍｅ）８０ｍｇをテトラヒドロフラン４０ｍｌに溶解し、室温撹拌下にＰ－Ｍｅ１００ｍｇおよび酢酸０．２ｍｌを加えて２週間反応させた。反応後、反応液を水洗後クロロホルム抽出し溶媒を留去後、酢酸エチル－メタノールにて再結晶化を行い、目的とするダイマー体ＭＨＰ$_2$（２）のテトラメチルエステルを得た。（１００ｍｇ，収率１３．９％）

【００４０】実施例　６

一段階法による同種二量体の合成

実施例１で得られたＰ－ＡｓｐＭｅ１００ｍｇをテトラヒドロフラン２５ｍｌに溶解し、室温撹拌下にアジピン酸ジヒドラジド（以下ＡＨと言う）を加え５日間反応させた。反応後、反応液を水洗し、クロロホルム抽出し溶媒を留去後、テトラヒドロフラン－酢酸エチル－ｎ－ヘキサンおよびメタノール－酢酸エチル－ｎ－ヘキサンにて再沈殿を繰り返し、黒褐色結晶のダイマー体ＡＨ（Ｐ－Ａｓｐ）$_2$（３）のオクタメチルエステルを得た。（５０ｍｇ，収率９．８％）

【００４１】実施例　７

実施例１で得られたＰ－ＡｓｐＭｅを各５０ｍｇ別々に採り、テトラヒドロフラン１０ｍｌと酢酸０．１ｍｌでそれぞれを溶解し、室温撹拌下にイソフタル酸ジヒドラジド（以下ｍＰＨと言う）およびテレフタル酸ジヒドラジド（以下ｐＰＨと言う）を各々に２０ｍｇ加えて２週間反応させた。反応後、それぞれの反応液を実施例６と同様に操作して後処理し、暗緑褐色結晶のダイマー体ｍＰＨ（Ｐ－Ａｓｐ）$_2$（４）およびｐＰＨ（Ｐ－Ａｓｐ）$_2$（５）のオクタメチルエステルを別々に得た。（３０ｍｇおよび３０ｍｇ、収率２１．２％および２１．２％）

【００４２】実施例　８

同種金属錯体の二量体化

実施例２で得られたＭｎ－Ｐ－Ｍｅ１００ｍｇとＭｎ－Ｐ－ＡｓｐＭｅ１４０ｍｇをそれぞれ別々に採り、前者にはテトラヒドロフラン１０ｍｌとＭＨ１０ｍｇ、後者にはテトラヒドロフラン４０ｍｌと酢酸０．５ｍｌ、ＡＨ５０ｍｇを加え、室温撹拌下に１週間反応させた。反応後、それぞれの反応液を前者の場合には実施例６、後者の場合には実施例５と同様に操作して後処理し、黒褐色結晶のダイマー錯体ＭＨ（Ｍｎ－Ｐ）$_2$（６）とＡＨ（Ｍｎ－Ｐ－Ａｓｐ）$_2$（７）のオクタメチルエステルを別々に得た。（７０ｍｇと７０ｍｇ、収率２６．８％と８．１％）

【００４３】実施例　９

二量体の同種金属錯体化

実施例６で得られた（３）のメチルエステル体を各５０ｍｇ別々に採り、これらをクロロホルム－メタノールにて溶解後、それぞれに酢酸銅および酢酸亜鉛を５０ｍｇ加えて室温撹拌下に１時間反応させた。反応後（反応液の色調およびＴＬＣにて確認）、それぞれの反応液を実施例３と同様に操作して後処理し、暗緑褐色結晶のダイマー錯体ＡＨ（Ｃｕ－Ｐ－Ａｓｐ）$_2$（８）とＡＨ（Ｚｎ－Ｐ－Ａｓｐ）$_2$（９）のオクタメチルエステルを別々に得た。（５０ｍｇと４５ｍｇ、収率９．２％と７．０％）

【００４４】実施例　１０

スピログラフィス　ジメチルエステル（以下ＳＰ－Ｍｅと言う）およびピロフェオホーバイジル－７－アスパラギン酸　ジメチルエステル（以下ｐｙｒｏＰＰＢ－ＡｓｐＭｅと言う）をそれぞれ別々に１００ｍｇ採り、以下それぞれを実施例６と同様に操作して後処理し、褐色結晶のダイマー体ＡＨ（ＳＰ）$_2$（１０）とＡＨ（ｐｙｒｏＰＰＢ－Ａｓｐ）$_2$（１３）のテトラメチルエステルをそれぞれ別々に得た。（５０ｍｇと４５ｍｇ、収率２２．０％と１６．７％）

【００４５】実施例　１１

モノマー金属錯体の合成

実施例２で得たＭｎ－Ｐ－Ｍｅ３００ｍｇおよび実施例

３で得たＣｕ－Ｐ－Ｍｅ２００ｍｇを別々に採り、前者にはテトラヒドロフラン９０ｍｌと６％MH水溶液１０ｍｌを、後者にはテトラヒドロフラン１５ｍｌと２％MH水溶液１０ｍｌを、加え室温撹拌下に３日間反応せしめた。以下それぞれを実施例４と同様に操作してピリジン－酢酸エチル－ｎ－ヘキサンにより再沈殿、再結晶化を行い、モノマー金属錯体マロン酸－モノ（Ｍｎ－フォトプロトポルフィリン　ジメチルエステル）ヒドラゾン［以下MH（Ｍｎ－Ｐ－Ｍｅと言う］とマロン酸－モノ（Ｃｕ－フォトプロトポルフィリン　ジメチルエステル）ヒドラゾン［以下MH（Ｃｕ－Ｐ－Ｍｅ）と言う］を別々に得た。（２５０ｍｇと１１０ｍｇ、収率５８．７％と４２．９％）

【００４６】実施例　１２

無金属－金属錯体における異種二量体の合成

実施例１１で得られたMH（Ｍｎ－Ｐ－Ｍｅ）およびMH（Ｃｕ－Ｐ－Ｍｅ）を各１００ｍｇ別々に採り、テトラヒドロフラン５０ｍｌと酢酸０．５ｍｌでそれぞれを溶解し、室温撹拌下に各々にＰ－Ｍｅ１５０ｍｇを加えて３日間反応させた。反応後（ＴＬＣ、ＵＶにて確認）、それぞれの反応液を酢酸エチルにて抽出し溶媒を留去後、酢酸エチル－ｎ－ヘキサンおよびメタノール－酢酸エチル－ｎ－ヘキサンにより再沈殿、再結晶を繰り返し、異種ダイマー体MH（Ｍｎ－Ｐ）（Ｐ）（１４）とMH（Ｃｕ－Ｐ）（Ｐ）（１５）のテトラメチルエステルを別々に得た。（５０ｍｇと４５ｍｇ、収率１６．９％と１５．２％）

【００４７】実施例　１３

実施例２で得たＭｎ－Ｐ－ＡｓｐＭｅ３００ｍｇおよび実施例３で得たＣｕ－Ｐ－ＡｓｐＭｅ１３０ｍｇをそれぞれ別々に採り、前者にはテトラヒドロフラン５０ｍｌおよび酢酸１０ｍｌを、後者にはテトラヒドロフラン２０ｍｌおよび酢酸０．２ｍｌを加え溶解し、２０％ＡＨ水溶液１０ｍｌを滴下し室温撹拌下に２時間反応せしめた。以下それぞれを実施例４と同様に操作してメタノール－酢酸エチル－ｎ－ヘキサンにて再沈殿、再結晶化を行い、それぞれのモノマー金属錯体アジピン酸－モノ（Ｍｎ－フォトプロトポルフィニル－６、７－ビスアスパラギン酸　テトラメチルエステル）ヒドラゾン［以下ＡＨ（Ｍｎ－Ｐ－ＡｓｐＭｅ）と言う］とアジピン酸－モノ（Ｃｕ－フォトプロトポルフィニル－６、７－ビスアスパラギン酸　テトラメチルエステル）ヒドラゾン［以下ＡＨ（Ｃｕ－Ｐ－ＡｓｐＭｅ）と言う］を別々に得た。（２００ｍｇと２０ｍｇ、収率１９．９％と４．５％）

【００４８】実施例　１４

実施例１３で得られたＡＨ（Ｍｎ－Ｐ－ＡｓｐＭｅ）５０ｍｇにテトラヒドロフラン３０ｍｌおよび酢酸０．５ｍｌ、Ｐ－ＡｓｐＭｅ５０ｍｇを、そしてＡＨ（Ｃｕ－Ｐ－ＡｓｐＭｅ）２０ｍｇにテトラヒドロフラン１５ｍｌ、酢酸０．５ｍｌおよびＰ－ＡｓｐＭｅ３０ｍｇを加えて室温撹拌下に２４時間反応させた。反応後、それぞれの反応液をクロロホルムにて抽出し０．９％生理食塩水で洗浄後溶媒を留去し、メタノール－酢酸エチル－ｎ－ヘキサンおよびメタノール－酢酸エチルにより再沈殿ならびに再結晶を繰り返し、異種のダイマー体ＡＨ（Ｍｎ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）（１６）およびＡＨ（Ｃｕ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）（１７）のオクタメチルエステルを別々に得た。（７０ｍｇと３５ｍｇ、収率１５．８％と４．４％）

【００４９】実施例　１５

ポルフィリン側鎖の違いにおける異種二量体の合成

Ｐ－Ｍｅ５００ｍｇにテトラヒドロフラン１００ｍｌおよび１％ＡＨ水溶液１００ｍｌを加えて室温撹拌下に２４時間反応させた。反応後、反応液を水洗しクロロホルムにて抽出し溶媒を留去後、メタノール－酢酸エチル－ｎ－ヘキサンにて数回再結晶化を行い、モノマー体アジピン酸－モノ（フォトプロトポルフィリン　ジメチルエステル）ヒドラゾン［以下ＡＨ（Ｐ－Ｍｅ）と言う］を得た。（３６０ｍｇ、収率５７．６％）ついで、得られた本モノマー体１５０ｍｇをテトラヒドロフラン５０ｍｌに溶解しこれにＰ－ＡｓｐＭｅ１５０ｍｇおよび酢酸０．２ｍｌを加えて４８時間室温撹拌下に反応させた。以下実施例６と同様に操作して後処理後、メタノール－酢酸エチル－ｎ－ヘキサンおよびクロロホルム－メタノールにて再沈殿、再結晶化を行い、異種ダイマー体ＡＨ（Ｐ）（Ｐ－Ａｓｐ）（１８）のヘキサメチルエステルを得た。（１１０ｍｇ、収率２０．０％）

【００５０】実施例　１６

ポルフィリン側鎖および金属の違いにおける異種二量体の合成

実施例２で得られたＭｎ－Ｐ－Ｍｅ２００ｍｇにテトラヒドロフラン１０ｍｌおよび１０％ＡＨ水溶液１０ｍｌを加えて室温撹拌下に２４時間反応させた。反応後、反応液を実施例１５と同様に操作後処理して、モノマー体アジピン酸－モノ（Ｍｎ－フォトプロトポルフィリン　ジメチルエステル）ヒドラゾン［以下ＡＨ（Ｍｎ－Ｐ－Ｍｅ）と言う］を得た。（２００ｍｇ、収率６７．１％）ついで、得られた本モノマー体１００ｍｇをテトラヒドロフラン２０ｍｌおよび酢酸０．２ｍｌに溶解し、これにＰ－ＡｓｐＭｅ１００ｍｇを加えて、以下実施例６と同様に操作して後処理後、異種ダイマー体ＡＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）（１９）のヘキサメチルエステルを得た。（１００ｍｇ、収率３３．６％）

【００５１】実施例　１７

Ｍｎ－Ｐ－Ｍｅモノマー誘導体の合成

実施例２で得られたＭｎ－Ｐ－Ｍｅ１５０ｍｇを２組採り、一方にはテトラヒドロフラン７．５ｍｌを加えて溶解し１０％ｍＰＨ水溶液を滴下し、他方にはテトラヒドロフラン１５ｍｌおよび５０％酢酸水溶液１５ｍｌにて

溶解しｐＰＨ７５０ｍｇを加えて、それぞれ別々に室温撹拌下に１時間反応させた。反応後、前者の反応液は実施例６と同様に操作し酢酸エチルーｎーヘキサンにて再沈殿精製して、モノマー体イソフタル酸ーモノ（Ｍｎーフォトプロトポルフィリン．ジメチルエステル）ヒドラジド［以下ｍＰＨ（Ｍｎ－Ｐ－Ｍｅ）と言う］を得た。（１２０ｍｇ、収率５２．４％）他方、後者を反応液は実施例３と同様に操作しメタノールーテトラヒドロフランークロロホルムー酢酸エチルにて再沈殿を繰り返し、モノマー体テレフタル酸ーモノ（Ｍｎーフォトプロトポルフィリン　ジメチルエステル）ヒドラジド［以下ｐＰＨ（Ｍｎ－Ｐ－Ｍｅ）と言う］を得た。（１５０ｍｇ、収率６５．６％）

【００５２】実施例　１８

実施例１７で得られたモノマーＭｎ錯体ｍＰＨ（Ｍｎ－ｐ－Ｍｅ）１００ｍｇおよびｐＰＨ（Ｍｎ－Ｐ－Ｍｅ）１５０ｍｇをそれぞれ別々に採り、一方はテトラヒドロフラン４０ｍｌおよび酢酸０．２ｍｌで溶解し実施例１で得られたＰ－ＡｓｐＭｅ１２０ｍｇを加え、他方はテトラヒドロフラン５０ｍｌおよび酢酸０．３ｍｌで溶解しＰ－ＡｓｐＭｅ１７０ｍｇを加え、室温撹拌下に２４時間反応させた。前者については反応後、反応液を実施例６と同様に操作し後処理後、テトラヒドロフラン一酢酸エチルーｎーヘキサンおよびメタノールー酢酸エチルーｎーヘキサンにより再沈殿、再結晶を繰り返し、異種ダイマー体ｍＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）（２０）のヘキサメチルエステルを得た。（８０ｍｇ、収率２１．２％）

他方後者については、反応後前述の（２０）の誘導体の場合と同様に操作して粗ｐＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）のヘキサメチルエステルを得た。（２００ｍｇ、収率４４．３％）得られたエステル体を引き続きそのままピリジンー苛性ソーダ水溶液中常法により加水分解後、中圧逆層カラムクロマトグラフィー（オクタデシルシリカゲル）に付しメタノールー水（４：１）画分を集め、溶媒を減圧留去後、ピリジンーメタノールにて再結晶化を行い、異種ダイマー体ｐＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）（２１）を得た。（８．８ｍｇ、収率２．１％）

【００５３】実施例　１９

Ｃｕ－Ｐ－Ｍｅモノマー誘導体の合成

実施例３で得られたＣｕ－Ｐ－Ｍｅ２００ｍｇを採り、テトラヒドロフラン１５ｍｌおよび１０％ＭＨ水溶液１０ｍｌを加えて２４時間、Ｃｕ－Ｐ－Ｍｅ２００ｍｇに、テトラヒドロフラン１５ｍｌおよび１０％ＡＨ水溶液１０ｍｌを加えて２４時間、Ｃｕ－Ｐ－Ｍｅ１５０ｍｇに、テトラヒドロフラン２２ｍｌ、メタノールー水混液１５ｍｌ、酢酸０．５ｍｌおよびｍＰＨ７５０ｍｇを加えて５分間、ならびにＣｕ－Ｐ－Ｍｅ１５０ｍｇに、テトラヒドロフラン４０ｍｌ、酢酸２０ｍｌおよびｐＰＨｌｇを加えて１時間、それぞれの４組を室温撹拌下に反応させた。反応後、それら４組の反応液それぞれにクロロホルムを加え水洗し溶媒を留去後、メタノールー酢酸エチルーｎーヘキサン、クロロホルムー酢酸エチルーｎーヘキサンおよび酢酸エチルーｎーヘキサン等で再沈殿、再結晶化を繰り返し行い、４種のモノマーＣｕ錯体４種すなわちマロン酸ー、アジピン酸ー、イソフタル酸ーおよびテレフタル酸ーモノ（Ｃｕーフォトプロトポルフィリン　ジメチルエステル）ヒドラゾン誘導体［以下ＭＨ（Ｃｕ－Ｐ－Ｍｅ）、ＡＨ（Ｃｕ－Ｐ－Ｍｅ）、ｍＰＨ（Ｃｕ－Ｐ－Ｍｅ）およびｐＰＨ（Ｃｕ－Ｐ－Ｍｅ）と言う］を別々に得た。（１１０ｍｇ、１６０ｍｇ、１４０ｍｇ、および７０ｍｇ、収率４２．９％、５９．３％、６７．５％および３３．８％）

【００５４】実施例　２０

実施例１９で得られたモノマーＣｕ錯体各４種［ＭＨ（Ｃｕ－Ｐ－Ｍｅ）１００ｍｇ、ＡＨ（Ｃｕ－Ｐ－Ｍｅ）１００ｍｇ、ｍＰＨ（Ｃｕ－Ｐ－Ｍｅ）１００ｍｇおよびｐＰＨ（Ｃｕ－Ｐ－Ｍｅ）５０ｍｇ］をそれぞれ別々に採り、前２者にテトラヒドロフラン２０ｍｌ、酢酸０．２ｍｌならびにＰ－ＡｓｐＭｅ１１０ｍｇを、後２者にテトラヒドロフラン４０ｍｌ、酢酸０．２ｍｌならびにＰ－ＡｓｐＭｅ１２０ｍｇおよびテトラヒドロフラン３０ｍｌ、酢酸０．２ｍｌならびにＰ－ＡｓｐＭｅ７０ｍｇを、加えて溶解し、室温２４時間撹拌下に反応させた。反応後、それぞれ４組の反応液を以下実施例１８と同様に操作して後処理し、酢酸エチルーｎーヘキサン、クロロホルムーｎーヘキサンおよびテトラヒドロフラン一酢酸エチルーｎーヘキサンにて再沈殿、再結晶を繰り返し行い、４種の異種ダイマー体ＭＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２２）、ＡＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２３）、ｍＰＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２４）およびｐＰＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２５）のヘキサメチルエステル体を得た。（１１０ｍｇ、９０ｍｇ、３０ｍｇおよび６０ｍｇ、収率２２．７％、２６．３％、１０．１％および４２．６％）

【００５５】実施例　２１

二量体の加水分解

実施例５で得られたＭＨ（Ｐ－Ｍｅ）$_2$（２）を常法によりピリジン中１０％苛性ソーダにて加水分解し、２０％クエン酸で中和後合成吸着剤に吸着し、水洗後、メタノールにて溶出した。溶出液を減圧濃縮乾燥後、メタノールー酢酸エチルにより再結晶化を行い、同種のダイマー体であるＭＨＰ$_2$（２）を得た。（加水分解による収率は８５．０％であった。）

以下他の二量体の加水分解はこれと同様に操作し後処理を行い、同種のダイマー体であるＯＨＰ$_2$（１）、ＡＨ（Ｐ－Ａｓｐ）$_2$（３）、ｍＰＨ（Ｐ－Ａｓｐ）$_2$（４）、ｐＰＨ（Ｐ－Ａｓｐ）$_2$（５）、ＭＨ（Ｍｎ－Ｐ）$_2$（６）、ＡＨ（Ｍｎ－Ｐ－Ａｓｐ）$_2$（７）、ＡＨ（Ｃｕ－Ｐ－Ａｓｐ）$_2$（８）、ＡＨ（Ｚｎ－Ｐ－

Ａｓｐ）$_2$（９）、ＡＨ（ＳＰ）$_2$（１０）、ＡＨ（ＳＰ－Ａｓｐ）$_2$（１１）、ＡＨ（ＰＰＢ）$_2$（１２）およびＡＨ（ｐｙｒｏＰＰＢ－Ａｓｐ）$_2$（１３）をそれぞれ得た。（これら加水分解による収率は８０～９５％であった。）

また、異種の二量体も先と同様に加水分解処理して異種のダイマー体であるＭＨ（Ｍｎ－Ｐ）（Ｐ）（１４）、ＭＨ（Ｃｕ－Ｐ）（Ｐ）（１５）、ＡＨ（Ｍｎ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）（１６）、ＡＨ（Ｃｕ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）（１７）、ＡＨ（Ｐ）（Ｐ－Ａｓｐ）（１８）、ＡＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）（１９）、ｍＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）（２０）、ＭＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２２）、ＡＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２３）、ｍＰＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２４）およびｐＰＨ（Ｃｕ－Ｐ）（Ｐ－Ａｓｐ）（２５）をそれぞれ得た。（これら加水分解による収率は８０～９５％であった。）

【００５６】実施例　２２

摘出器官でのレーザー照射（励起蛍光スペクトル）

ニトロソアミン発癌の膵癌細胞を移植した１４～２１日目のゴールデンハムスター（１群五匹）にリン酸緩衝液（１ｍｌ）にて希釈した５ｍｇの被験薬剤ｍＰＨ（Ｍｎ－Ｐ）（Ｐ－Ａｓｐ）（２０）を静注後、癌を含む各臓器を摘出し、得られた各器官にN_2－ｐｕｌｓｅｄ　ｌａｓｅｒ（N_2、３３７ｎｍ、２ｎｓ、４００～１０００ｎｍ）を照射し、励起蛍光スペクトルを測定し、４７０ｎｍのＮＡＤＨのピーク波長を基準として　６００～９００ｎｍの波長を検討した。（N_2－ＰＬＳ測定）

以下同様にして得られた結果（癌／各臓器　比）を表２に示す。表２は薬剤投与６時間後に摘出した各器官の各励起蛍光スペクトルを測定し、４７０ｎｍのピーク波長を基準１として６００～９００ｎｍでのピーク波長を算出した値を示す。なお、同種のダイマーＭｎ錯体（例えば化合物６や７）は蛍光が無くN_2－ＰＬＳ測定ができなかった。

【００５７】

【表２】

化合物名	癌／臓器			
	癌／肝	癌／肺	癌／胃	癌／血清
(3) AH(P-Asp)$_2$	3.29	3.37	3.29	0.25
(9) AH(Zn-P-Asp)$_2$	2.55	3.92	3.33	0.31
(16) AH(Mn-P-Asp)(P-Asp)	1.68	3.08	4.11	0.46
(17) AH(Cu-P-Asp)(P-Asp)	4.16	4.65	8.78	1.39
(18) AH(P)(P-Asp)	1.89	4.14	3.63	0.39
(19) AH(Mn-P)(P-Asp)	2.62	3.80	5.07	0.60
(20) mPH(Mn-P)(P-Asp)	4.00	4.17	7.14	0.30
(21) pPH(Mn-P)(P-Asp)	3.05	2.68	3.53	0.42
(24) mPH(Cu-P)(P-Asp)	6.57	4.31	6.27	0.35

【００５８】実施例　２３

ダンシルメチオニンを用いる光増感酸化反応の評価

基質（ダンシルメチオニン）１０μＭをクロロホルム１ｍｌに溶解し、前記実施例で得られた増感剤０．１μＭを加え、撹拌下にＣｏｌｄ　Ｓｐｏｔ　ＰＩＣＬ－ＳＸ（Ｎｉｐｐｏｎ　Ｐ．Ｉ．Ｃｏ．Ｌｔｄ）（ハロゲンランプ、１５０Ｗ、８０，０００Ｌｕｘ）で照射した。光照射１分毎に反応液をＴＬＣ板（Ｋｉｅｓｅｌｇｅｌ　６０Ｆ$_{254}$）にスポットし、クロロホルム－メタノール（３：２）で展開後、ＵＶランプ（２５４ｎｍ）でダンシルメチオニンとその酸化生成物（ダンシルメチオニン　スルホキシド）をチェックした。ＴＬＣ板上でダンシルメチオニンが完全に消失した時間を反応終了時間とし、各増感剤の光酸化反応の強弱を比較検討した。その結果を図１および表３に示す。なお、図１中縦軸はＲｆを横軸は時間（分）を示し、Ｒｆ値０．７９はダンシルメチオニン、０．４３はダンシルメチオニン　スルホキシドのスポットである。また、表３の数値は反応完了時

間を分で示し、この値（分）が小さければ小さいほど光酸化反応が強いことを意味する。

【００５９】

【表３】

化合物名	光反応の強さ
MHP	2
PhotofrinII®	10＜
(2) MHP_2	2
(3) AH (P－Asp)$_2$	2
(4) mPH (P－Asp)$_2$	3
(5) pPH (P－Asp)$_2$	3
(9) AH (Zn－P－Asp)$_2$	3
(14) MH (Mn－P) (P)	－
(16) AH (Mn－P－Asp) (P－Asp)	－
(17) AH (Cu－P－Asp) (P－Asp)	10＜
(20) mPH (Mn－P) (P－Asp)	－
(22) MH (Cu－P) (P－Asp)	10＜
(24) mPH (Cu－P) (P－Asp)	10＜

【００６０】実施例　２４

質量分析

ＦＡＢ質量分析法により本誘導体の質量を測定した。その測定結果の代表例として、MHP_2（２）、MH（Mn－P）$_2$（６）、AH（Mn－P－Asp）（P－Asp）（１６）およびAH（Cu－P－Asp）（P－Asp）（１７）のメチルエステル体のＦＡＢ質量分析スペクトルを図２、図３、図４および図５に示す。

【００６１】実施例　２５

紫外線吸収スペクトル分析（アルブミンテスト）

ポルフィリン化合物はアルブミン溶液中で、二単量体あるいは多量体を形成することが知られている。この性質はアルブミン濃度を種々変えて分析を行うことで極大吸収値の移動または吸光係数の変動がみられることで判かる。したがって癌細胞との親和性を検討するには簡単なスクリーニングテストである。アルブミン５４ｍｇを３ｍｌの生理食塩水に溶解し、１．８％濃度とする。次いでこれを１０倍希釈して０．１８％とした液を公比３で希釈して各アルブミン濃度（１．８、０．１８、０．０６、０．０２、０．００６６、０．００２２％）の液を調製した。一方、ポルフィリン誘導体１ｍｇをリン酸緩衝液（ｐＨ８．０）１ｍｌに溶解し、生理食塩水で１００ｍｌにした。そしてアルブミン希釈液２ｍｌとポルフィリン溶液２ｍｌを混合し、混液のアルブミン最終濃度を０．９、０．０９、０．０３、０．０１、０．００３３、０．００１１％とし紫外線吸収スペクトル測定（３５０～９００ｎｍ）を行った。またアルブミン希釈液のかわりに生理食塩水およびメタノール溶液中でも同様に測定した。これらの測定結果を表４に示す。その代表例として、AH（P）（P－Asp）（１８）の紫外線吸収スペクトルを図６および図７に示す。

【００６２】

【表４】

23　　24

化合物名	波長（nm）		
	生理食塩水	メタノール	0.9％アルブミン
(3) AH(P-Asp)$_2$	677	675	678
(7) AH(Mn-P-Asp)$_2$	682	676	679
(9) AH(Zn-P-Asp)$_2$	653	653	655
(16) AH(Mn-P-Asp)(P-Asp)	677	676	678
(17) AH(Cu-P-Asp)(P-Asp)	677	677	678
(18) AH(P)(P-Asp)	681	679	683
(19) AH(Mn-P)(P-Asp)	677	676	679
(20) mPH(Mn-P)(P-Asp)	678	674	680
(22) MH(Cu-P)(P-Asp)	674	673	676
(23) AH(Cu-P)(P-Asp)	674	673	673
(24) pPH(Cu-P)(P-Asp)	674	673	677

【００６３】

【発明の効果】本発明のあるポルフィリン誘導体は癌細胞への集積性、外部エネルギーに対する反応性ならびに癌細胞の破壊作用を有し、またある誘導体は無燐光性あるいは無燐光無蛍光性を有し、しかも正常細胞に対して毒性を発現することがないことから目的に応じて化合物が対応できるので、癌治療薬あるいは癌診断薬として究めて有用である。

【図面の簡単な説明】

【図１】ＡＨ（Ｐ－Ａｓｐ）$_2$（３）オクタメチルエステルを増感剤として用いた薄層クロマトグラムを示す図である。

【図２】ＭＨＰ$_2$（２）テトラメチルエステル（$C_{75}H_{80}N_{12}O_{12}$、１３４０．６）の質量分析スペクトル（ＦＡＢ－ＮＢＡ）を示す図である。

【図３】ＭＨ（Ｍｎ－Ｐ）$_2$（６）テトラメチルエステル（$C_{75}H_{82}N_{12}O_{16}Mn_2$、１５１６．４）の質量分析スペクトル（ＦＡＢ－ＮＢＡ）を示す図である。

【図４】ＡＨ（Ｍｎ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）（１６）オクタメチルエステル（$C_{98}H_{115}N_{16}O_{26}Mn$、１９８６．８）の質量分析スペクトル（ＦＡＢ－ＮＢＡ）を示す図である

【図５】ＡＨ（Ｃｕ－Ｐ－Ａｓｐ）（Ｐ－Ａｓｐ）（１７）オクタメチルエステル（$C_{98}H_{112}N_{16}O_{24}Cu$、１９５９．７）の質量分析スペクトル（ＦＡＢ－ＮＢＡ）を示す図である

【図６】ＡＨ（Ｐ）（Ｐ－Ａｓｐ）（１８）の紫外線吸収スペクトルを示す図である。

【図７】ＡＨ（Ｐ）（Ｐ－Ａｓｐ）（１８）の紫外線吸収スペクトルを示す図である。

【符号の説明】

１　ポルフィリン溶液と生理食塩水の混液（アルブミン濃度０％）

２　ポルフィリン溶液とアルブミン溶液の混液（アルブミン濃度０．００１１％）

３　ポルフィリン溶液とアルブミン溶液の混液（アルブミン濃度０．００３３％）

４　ポルフィリン溶液とアルブミン溶液の混液（アルブミン濃度０．０１％）

５　ポルフィリン溶液とアルブミン溶液の混液（アルブミン濃度０．０３％）

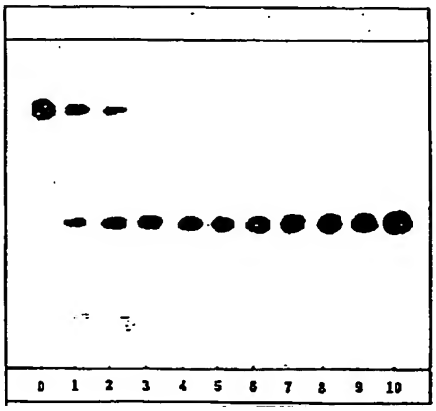
６　ポルフィリン溶液とアルブミン溶液の混液（アルブミン濃度０．０９％）

７　ポルフィリン溶液とアルブミン溶液の混液（アルブミン濃度０．９％）

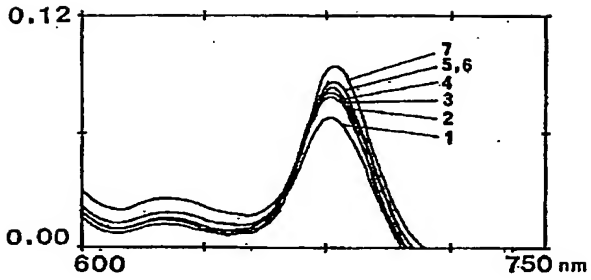
25　　26

8　ポルフィリン溶液とメタノールの混液

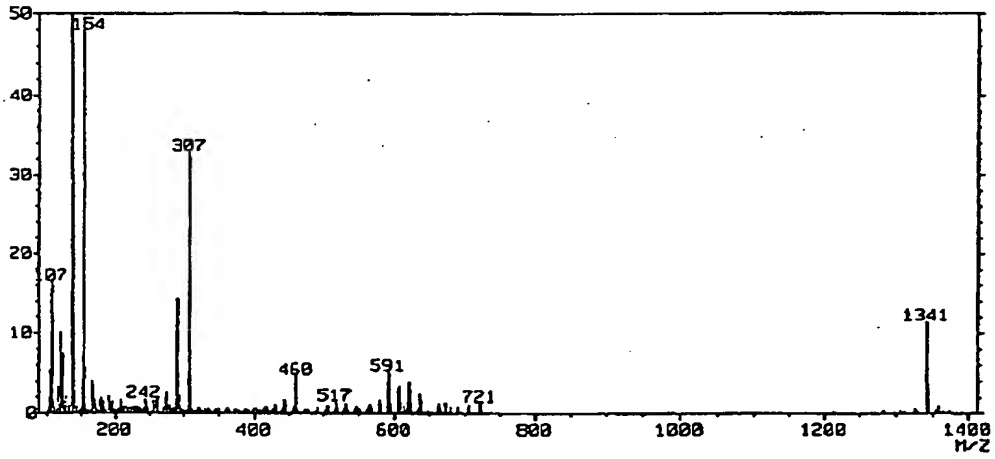
【図１】



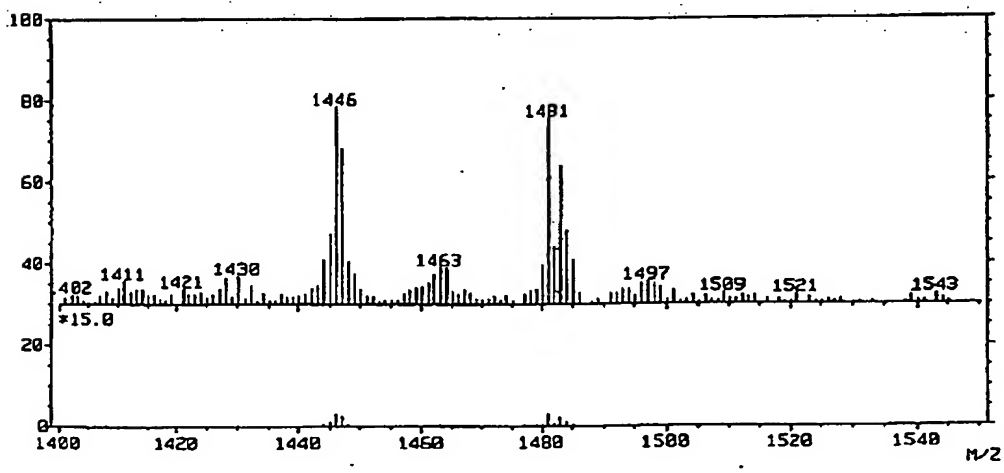
【図６】



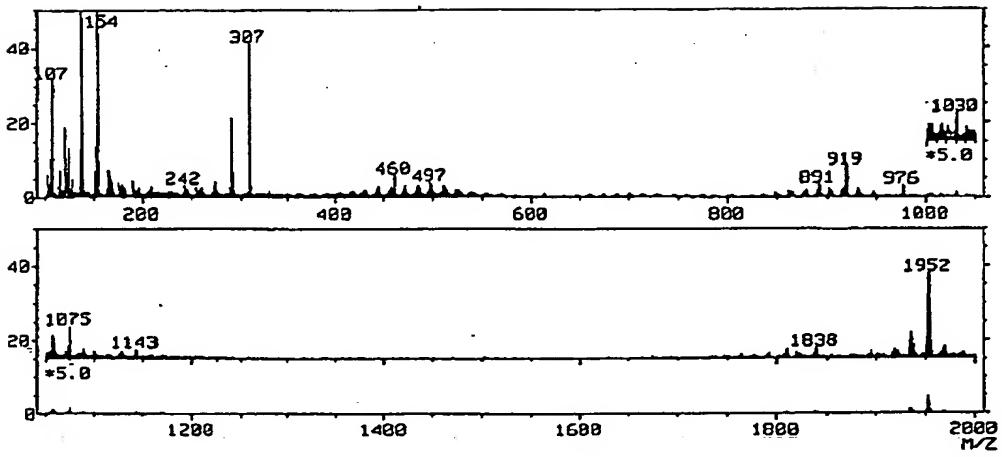
【図２】



【図３】



【図４】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242
460
497
919
891
976
200
400
600
800
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1952
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1143
1838
*5.0
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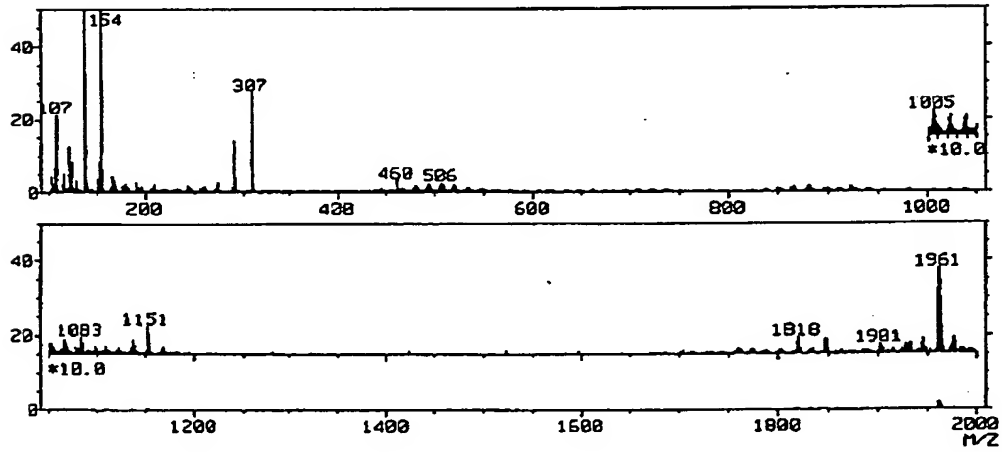
【図５】


154
307
107
1005
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400
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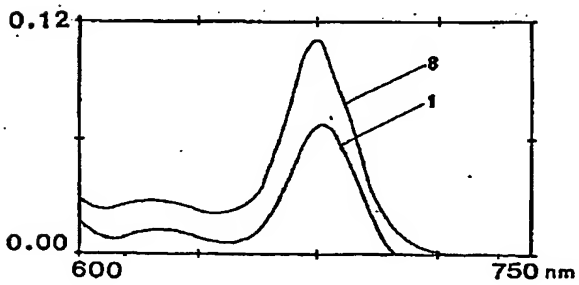
800
1000
1961
1083
1151
1818
1901
*10.0
1200
1400
1600
1800
2000
M/Z

【図７】


0.12
0.00
8
1
600
750 nm